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1. Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• HEMORRHAGIC TELANGIECTASIA

Q. I would appreciate information on the differential diagnosis and treatment of congenital hereditary telangiectasia.

M.D.—Pennsylvania

A. Hereditary hemorrhagic telangiectasia is an inherited abnormality which may affect either sex. It appears at puberty or thereafter and characteristically involves the skin and mucous membranes; any of the viscera may be affected also. Although the usual presenting symptom is epistaxis, hemorrhages may occur at any site along the alimentary, respiratory and urinary tracts. Hidden hemorrhages also may occur, for example, in the region of the central nervous system. Occasionally, a pulmonary arteriovenous fistula develops. Secondary anemia is a frequently occurring complication.

Other telangiectatic and hemorrhagic conditions must be considered in making a differential diagnosis. The former include the nevus araneus of pregnancy and liver disease; senile ectasias; telangiectatic changes in actinodermatitis, rosacea, erythema ab igne, scleroderma and poikilodermatous states; and generalized idiopathic telangiectasia. Blood dyscrasias and coagulation defects can be ruled out.

Treatment consists of hemostasis, supplemented by transfusions when necessary. Other measures employed in the past included use of radium, radiation therapy to the spleen, electrocautery and chemical cautery, and intranasal surgical procedures, especially submucous resection; administration of vitamin K, rutin and iron; and injection of moccasin venom.

• CORTISONE IN CORONARY INSUFFICIENCY

Q. A middle-aged, obese woman has arthritis of the cervical spine, resulting from a whiplash injury sustained in a car accident. I have hesitated to prescribe cortisone because she has coronary insufficiency. Is it safe to give cortisone when coronary insufficiency is present?

M.D.—Ohio

A. In my opinion it is safe to use cortisone, when indicated, in the presence of coronary insufficiency.

• IODINE IN HYPOTHYROIDISM

Q. Is iodine therapy of any type contraindicated in hypothyroidism? I realize that iodine will decrease the output of an overactive thyroid, but I also thought that iodine would normalize a subsecreting gland.

M.D.—Ohio

A. Large doses of iodine decrease the output of thyroid hormone. Of course, this is much more striking in the hyperplasia of Graves' disease than in the normal gland; however, I do not find any evidence that large doses of iodine ever stimulate the function of the thyroid. Certainly, in the most common cause of hypothyroidism, struma lymphomatosa, iodine therapy appears to increase the thyroid failure and often results in a rapid compensatory enlargement of the goiter and an increase of the clinical hypothyroidism. Therefore, I believe that iodine therapy is contraindicated in hypothyroidism.

(Continued on page A-20)

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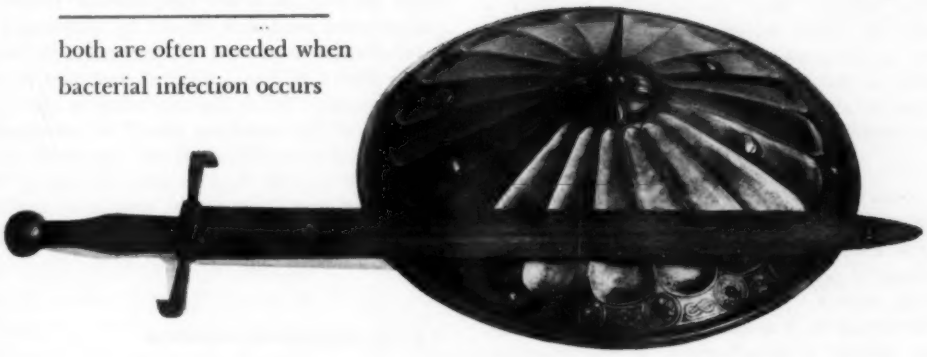

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• BRONCHIAL ASTHMA

Q. A 46 year old man has had bronchial asthma since 1947. He has used ephedrine inhalers, TEDRAL®, DORSAMIN®, HYDRILLIN® Compound, potassium iodide, Quadrinal and various antihistaminic preparations. He also received x-ray therapy during 1955, 1956 and 1958 and has been given ACTH injections to relieve the more severe attacks. More recently, he received a course of several injections of PIROMEN®; however, at the present time drugs give him only partial or temporary relief. He has no history of specific allergy. What further treatment would you advise?

M.D.—Colorado

A. This history is typical of the person who seeks to cure his asthma without having proper studies made. He has been given the very best medication possible, but unfortunately that is not the answer.

He should be hospitalized and have thorough x-ray studies, a bronchogram, a bronchoscopic examination, blood studies and an allergy study with both scratch and intradermal tests. If necessary, he should be placed on an elimination diet.

• TESTS AND EQUIPMENT

Q. Do the URISTIX®, KETOSTIX®, ALBUSTIX® and CLINISTIX® tests deteriorate with time and exposure to air or sunshine, or both? Prior to use, is it possible to tell whether or not the test strips are reliable? Would deterioration cause a change in test results?

Are kitchen pressure cookers adequate for sterilizing instruments, rubber gloves and syringes? Is it advisable to use a pressure cooker rather than to boil syringes?

Inexpensive polyethylene sheets would make excellent disposable drapes for minor surgical procedures. Can they be sterilized?

M.D.—Nova Scotia

A. To determine whether or not test strips are reliable, test an old strip at the same time as a fresh one. The older paper may have become dry and will therefore absorb fluid more slowly.

Pressure cookers are good office sterilizers; however, syringes and needles usually can be sterilized by boiling.

Although polyethylene sheets are clean, they probably cannot be sterilized. Lay sterile gauze over them.

• UMBILICAL HERNIA

Q. When is umbilical hernia in a child treated surgically?

M.D.—Montana

A. Umbilical hernia in a child during the first year of life is usually treated conservatively, since the development of the abdominal musculature often renders the defect insignificant. However, conservative treatment should be abandoned if incarceration is present. If the defect is much larger than 1 to 2 cm., surgical treatment is usually necessary. When this procedure is used, the anatomy of the umbilicus should be preserved.

Repair of an umbilical hernia is probably more imperative in girls than in boys because of the subsequent stress imposed by pregnancy and the known increase of complications of umbilical hernia in adult women.

• BLOOD TRANSFUSION IN CHILDREN

Q. What criteria should be used in giving blood transfusions to infants and children? Should blood or orally administered iron be given to a three year old child who is not acutely ill but who has a 30 per cent hemoglobin level as a result of hookworm disease? What hemoglobin level, clinical findings and age level should influence the giving of blood? I am concerned about the danger of transfusion reactions.

M.D.—Puerto Rico

A. The first consideration in the criteria for blood transfusions in children is to eradicate the cause of the anemia, in this case the hookworm infection. Meanwhile, there is no contraindication to giving a blood transfusion, since it would increase the blood content and relieve the anemia more quickly than orally administered iron.

If the child is able to take iron orally, an arbitrary hemoglobin level of 7 gm. may be used, below which a blood transfusion may be justified; a higher hemoglobin level would suggest the use of orally administered iron in a therapeutic dosage.

In giving a blood transfusion to an infant or a small child, the risk of transfusion reactions must be weighed against the dangers inherent in prolonged anemia which may be more quickly corrected by administering blood. The amount of blood given usually does not exceed 10 cc. per pound of body weight.

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1. Johnson, J. F.: Proc. Soc. Exper. Biol. & Med. 94:92 (Jan.) 1957. 2. Idem: Paper presented at Symposium on Blood, Wayne State Univ., Detroit, Mich., Jan. 18, 1957. 3. Owren, P. A.: Northwest Med. 56:31 (Jan.) 1957. 4. Published and unpublished case reports.

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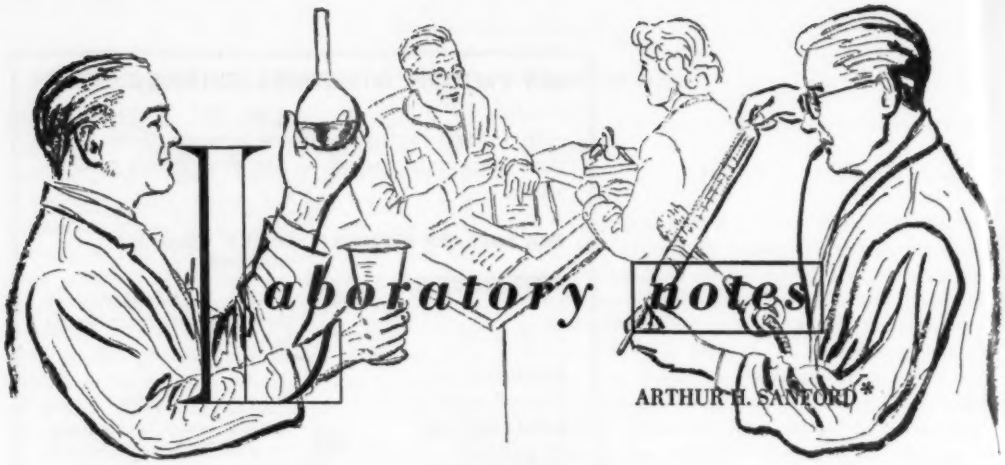

ARTHUR H. SANFORD*

Hyperparathyroidism

RECENTLY the following inquiry was received from a subscriber to POSTGRADUATE MEDICINE: "What laboratory procedures are considered most useful in making a diagnosis of hyperparathyroidism?"

The function of the parathyroid glands must be kept in mind. The protein hormone from these glands affects the regulation of calcium and inorganic phosphorus metabolism. Derangement of secretion of this hormone may bring about quite a chain of disorders which can be shown by clinical laboratory tests.

The most usual pathologic lesion of these glands is adenoma. Hypertrophy or hyperplasia accounts for hyperparathyroidism in a small number of instances, and carcinoma does occasionally occur in this region.

When there is excessive production of parathyroid hormone, increased excretion of inorganic phosphorus in the urine follows, with a loss of serum phosphorus. The amount of serum calcium increases, and excessive amounts of calcium are excreted in the urine.

The excessive excretion of calcium may damage the kidney, and renal calculi may form. It has been stated that about 5 per cent of all renal calculi may be due to hyperparathyroidism. Renal disease without pathologic change in the bone may be misleading, and the pathologic condition in the parathyroid glands may not be suspected. Sodeman[1] stated that four different types of clinical pathologic change could actually be found: (1) chemical hyperparathyroidism without disease of the bone or kidney, (2) hyperparathyroidism with disease of the bone but without disease of the kidney, (3) hyperparathyroidism with disease of the kidney but without disease of the bone, and (4) hyperparathyroidism with disease of both the kidney and bone.

It is obvious, then, from this brief discussion of the pathologic physiology of the parathyroids resulting in increased production of the hormone that certain tests should be performed for purposes of diagnosis.

Serum inorganic phosphorus tests should be carried out. The normal value in adults varies from 3 to 5 mg. per 100 cc. In infants and growing children, levels are higher, 4 to 7 mg. per 100 cc. In primary hyperparathyroidism, the first change may be a lowering of the level to 2 mg. or less per 100 cc. If this persists in subsequent tests, it may be highly suggestive of this disease.

Serum calcium levels normally range from 9 to 11 mg. per 100 cc. In hyperparathyroidism, values may be as high as 16 to 18 mg. per 100 cc. The calcium is rapidly removed through the urine and feces. Accurate determinations of the amount excreted are very difficult procedures and are not called for.

(Continued on page A-28)

*Emeritus Staff, Section of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.

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Sulkowitch's test may be used to advantage in diseases of the parathyroid. The patient should be kept on a low calcium diet (no milk, milk products or nuts) for three days. A strongly positive reaction indicates hypercalcemia consistent with hyperparathyroidism.

The reagent for Sulkowitch's test contains 2.5 gm. oxalic acid, 2.5 gm. ammonium oxalate, 5 cc. glacial acetic acid and 150 cc. distilled water; 5 cc. of reagent is added to 5 cc. centrifuged urine. The density of the cloud is noted after mixing and allowing the mixture to stand for two minutes. The results are recorded as:

0	clear
1 +	slight cloud
2 + +	moderate cloud
3 + + +	heavy cloud
4 + + + +	solid cloud

Hypocalcemia (less than 7.5 mg. per 100 cc.) is indicated if the result is zero. Hypercalcemia is evidenced by 3 plus or 4 plus and indicates more than 11 mg. calcium per 100 cc. The test is strongly positive in hyperparathyroidism, Paget's disease of bone, and severe osteoporosis. This simple test is probably not performed as often as it should be for the detection of possible hyperparathyroidism.

Renal insufficiency due to this disease is characterized by all the findings in urinalysis of generalized renal insufficiency, namely, red blood cells, pus cells, albumin and casts. Calcium casts may be found. Renal disease contraindicates surgical treatment of disease of the parathyroid.

If more elaborate methods of study of this condition seem advisable, the reader may be interested in the tests for hyperparathyroidism dealing with tubular reabsorption of phosphate, phosphate deprivation and calcium infusion reported by Chambers and co-workers.[2]

REFERENCES

1. Sodeman, W. A.: Pathologic Physiology. Philadelphia and London, W. B. Saunders Company, 1956, p. 147.
2. Chambers, E. L., Jr., Gordan, G. S., Goldman, L., Reifenstein, E. C., Jr., Omi, J. and Martinez, E.: Tests for hyperparathyroidism: Tubular reabsorption of phosphate, phosphate deprivation and calcium infusion. J. Clin. Endocrinol. 16:1507-1521 (November) 1956.

What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

FINGER-PRICK TEST FOR SYPHILIS

American Society of Clinical Pathologists:

• A satisfactory flocculation test for syphilis, using unheated serum or plasma, requires only a drop of blood pricked from the finger. The answer is yielded in as little as eight minutes. The test is offered only as a screening procedure. Due to its hypersensitivity, it may record false positive rather than false negative reactions. Treatment should be started only after the positive reaction is confirmed by one of the older tests.—Dr. John J. Andujar, Department of Health Laboratories, Fort Worth.

• Steps to decrease risk of unfavorable reaction to blood transfusions: (1) As the transfusion is to be started, fresh samples drawn directly from the donor unit and the patient are regrouped and Rh-typed, thus allowing detection at the bedside of major incompatibilities from previous misidentification of tubes or patients. (2) Smear from the donor blood is examined for bacteria at the bedside. (3) A specially trained nurse is on duty to detect manifestations of reaction at the earliest possible moment. (4) A sample of the patient's blood is drawn following the transfusion.—Dr. Frank R. Dutra, Castro Valley, Calif.

USE AND ABUSE OF ANTIPYRETIC THERAPY

American Academy of Pediatrics:

• Fever, although only a symptom, is usually fought as though it were a disease. Measures aimed at promoting its artificial reduction eliminate fever as a diagnostic aid and as a valuable indicator of both therapeutic response and the occurrence of complications. Fever may possibly increase body defenses as well. Simple measures to enhance body heat loss, such as thinner clothing and more air circulation, should be tried first. If additional measures are needed, sponge baths with tepid water are preferable to antipyretic drugs, since better control of reduction is possible.—Dr. Alan Done, University of Utah College of Medicine, Salt Lake City.

• Newly isolated type 1 and type 2 hemadsorption viruses may be causing between 6 and 18 per cent of all respiratory tract illnesses in children. They are found most often in children less than one year old, but they also are found in those through the age of 10. Cough and sore throat are the major symptoms. In the more severely ill, abnormal lung findings may be present.—Dr. Robert H. Parrott, Children's Hospital, Washington, D.C.

• Norethandrolone significantly stimulates appetites of children with weight lag. It is chemically related to testosterone but has only 6 per cent of its androgenic effect, while the anabolic effect is unchanged.—Dr. Samuel S. Brown, Jewish Hospital, Brooklyn.

HYPERTENSION LINKED TO ENZYME

American Heart Association, scientific session:

• Studies on patients suggest that a deficiency of the recently discovered enzyme *O*-methyl-transferase may be the initiating cause of primary hypertension. The deficiency appears to be hereditary. This would not preclude the addition of renal and arteriosclerotic factors as the disease progresses.—Dr. Milton Mendlowitz, Mount Sinai Hospital, New York.

• While nitroglycerin is without equal for an acute attack of angina pectoris, erythrityl tetranitrate administered sublingually or pentaerythrityl tetranitrate given orally is valuable for prolonged prophylactic therapy.—Dr. Henry I. Russek, Staten Island.

NEW LUNG SYNDROME

American Roentgen Ray Society:

• The name "idiopathic unilateral hyperlucency of the lung" has been selected to describe a syndrome in which there is an abnormal degree of radiolucency. A small number of such cases have been observed which do not fall among the usual pulmonary entities. The involved lung retains its radiolucency on expiration and is associated with a mediastinal shift identical to that seen in obstructive emphysema. Yet the main bronchus supplying the affected portion of the lung is normal in caliber. Cough, expectoration and wheezings, along with labored breathing and bloody saliva, are common findings in all patients.—Dr. Harold N. Margolin, Cincinnati.

• Endarterectomy of a partially occluded carotid vessel has been performed in 28 persons following angiographic examination. It is readily apparent that the patient with severe stenosis almost always can be improved beyond even any spontaneous recovery that may occur.—Drs. Marvin M. Keirns and John E. Whiteleather, Memphis.

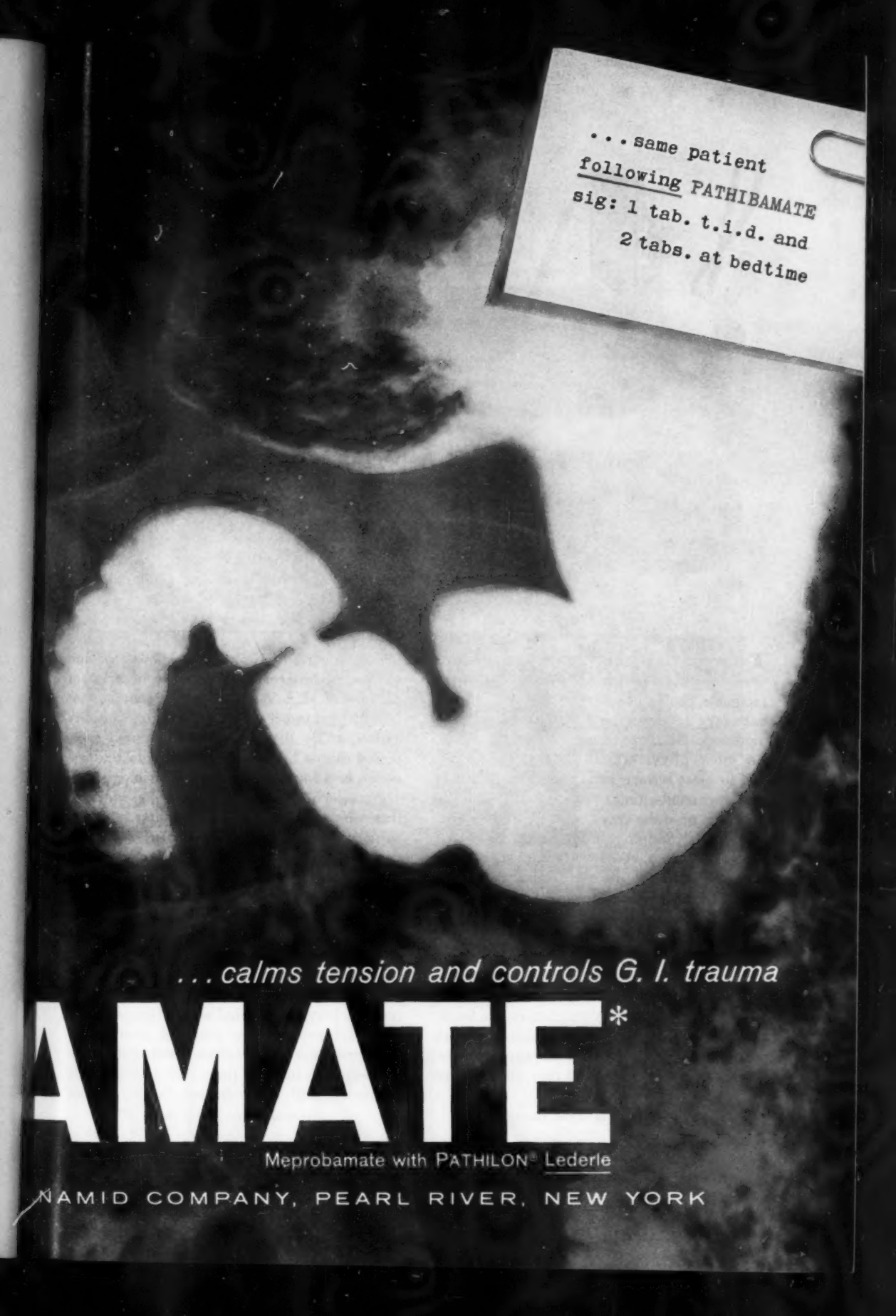
• Evidence of pulmonary embolism is reported in 10 to 25 per cent of necropsies. Unfortunately, in many hospitals and in office practice it often goes unrecognized. Clinically, embolic episodes are commonly misdiagnosed as pleurisy, pneumonia or coronary artery disease. It is evident from experience in many hospitals that the frequency with which pulmonary embolism is clinically diagnosed depends largely on the frequency with which the radiologist calls attention to it.—Dr. George N. Stein, Philadelphia.

TUMORS BLOCKED BY VIRUS

American Public Health Association:

• Tumors induced in hamsters by the polyoma virus can be prevented by an immunizing agent prepared from the virus. Hamsters were injected with the immunizing agent when they were two days old and again when eight days old. When the hamsters were subsequently challenged with live virus two weeks later, tumors did not develop in 97 per cent. Sixty-seven per cent of the nonimmunized control litter mates died with tumors within five months. At present, there is no evidence to show implications of this work in preventing human cancer.—Dr. Sarah E. Stewart, National Cancer Institute, Bethesda.

• Preliminary results of a continuing study of insulin treatment for apparently prediabetic women during pregnancy are indicating a reduction in incidence of fetal abnormalities and large babies. Glucose tolerance tests are imperative in each trimester. About 1 per cent of women with negative findings in the first trimester had positive findings in the second. Eight per cent with negative findings in the first or second trimester had positive findings in the third.—Dr. Hugh C. Wilkerson, United States Public Health Service, Washington, D.C.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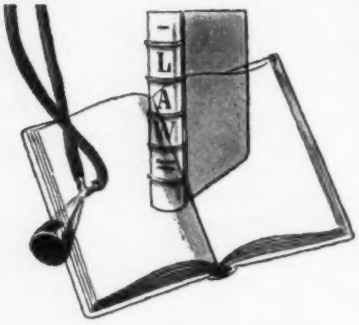

Forensic Medicine

Some Medicolegal Aspects of Anesthesiology

M. C. SLOUGH*

University of Kansas School of Law, Lawrence

M. C. SLOUGH

THE word "malpractice" represents an unfortunate choice of vocabulary to describe professional liability. To most physicians, and to most laymen as well, it connotes a moral wrong, or at the very least gross incompetence on the part of the professional defendant. The term "professional tort liability" would be less inciting and it certainly would be more appropriate.

Obviously a physician is not an insurer of success; hence persons administering anesthetics in the course of medical treatment are not insurers against harm or guarantors of a favorable result. Those who undertake any work calling for special skills are required to exercise reasonable care in what they do and must possess a certain minimum of knowledge and ability. Allowances must be made in terms of degrees of skill. A rural practitioner cannot be expected to act with the precision of a city specialist. By the same token, a nurse anesthetist cannot be expected to act with the precision of a highly trained anesthesiologist.

New technics and developments in anesthesia have increased the scope and safety of surgery, yet it cannot be denied that new drugs, appliances and technics have created new risks of accidental overdosage, undue sensitivity, and other hazards previously unknown to medical science. In the administration of an anesthetic, even comparatively minor degrees of lack of skill can result in most serious consequences. What may have been regarded as normal procedure a generation ago may be regarded as negligence today.

To achieve a more practical analysis of legal problems that face the anesthetist or anesthesiologist in these times, the scope of this discussion will be dedicated largely to an

(Continued on page A-38)

*Dean, University of Kansas School of Law, Lawrence, Kansas.

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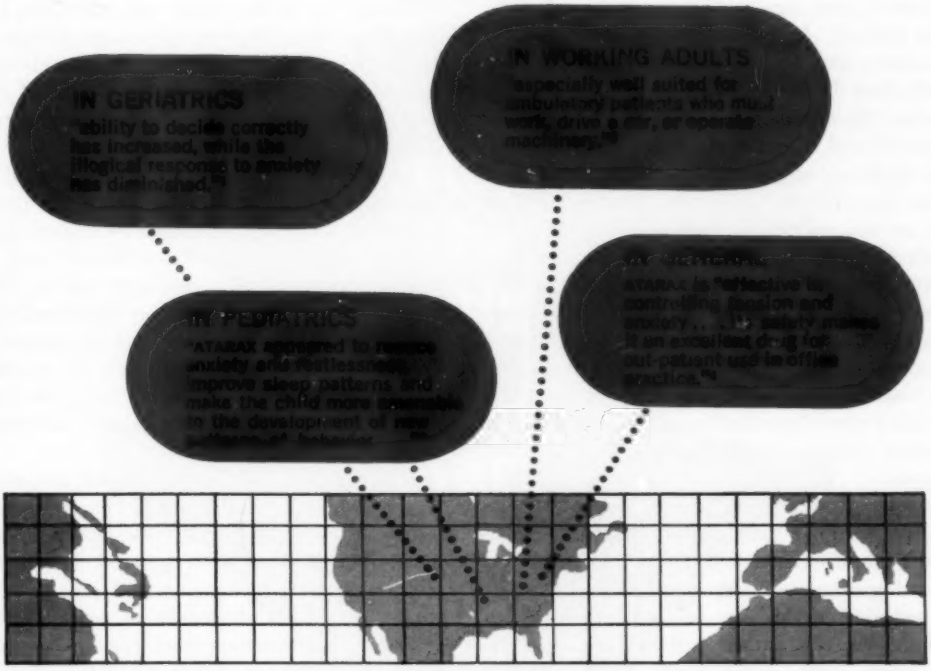
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References: 1. Smigel, J. O., et al.: J. Am. Ger. Soc., in press. 2. Freedman, A. M.: Pediat. Clin. North America 5:573 (Aug.) 1958. 3. Ayd, F. J., Jr.: New York J. Med. 57:1742 (May 15) 1957. 4. Menger, H. C.: New York J. Med. 58:1684 (May 15) 1958. 5. Colrault, M., et al.: Presse méd. 64:2239 (Dec. 26) 1956. 6. Bayart, J.: Presented at the International Congress of Pediatrics, Copenhagen, Denmark, July 22-27, 1956.

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analysis of specific case studies. Reference will be made to five separate appellate opinions bearing on the rights, privileges and duties of persons within the profession.

*Ayers vs. Parry**

This case originated in the United States District Court for the District of New Jersey. The patient, Ayers, underwent an operation to correct obstruction of the common bile duct. Defendant Parry was the surgeon, defendant Haines the anesthesiologist. Spinal anesthesia was selected because the physicians were of the opinion that ether would be harmful to the liver. Dr. Haines inserted the needle between the second and third lumbar vertebrae, and during the operation gas, oxygen and ether complemented the spinal injection. At the moment the fluid was injected, Ayers complained of a jabbing pain down the right leg. He screamed and lost consciousness. Next day he could not move his leg, and examination revealed partial paralysis, marked atrophy and sensory changes in the leg and the adjacent organs.

At trial, one expert witness, an anesthesiologist, testified that pain normally resulted when the needle struck the nerve roots. A neurologist subsequently testified that a painful reaction of this sort was a common experience, that this patient suffered an injury to the nerve roots in the cauda equina. Nerve roots were injured on the right side from the eleventh thoracic down to the fifth sacral nerve root. The neurologist further testified that the anesthetic agent had a toxic effect on these nerve roots, causing paralysis, atrophy and sensory changes.

The treating physician, on cross-examination, agreed that the unfavorable reaction was something that could not be predetermined, that it was one of the hazards of anesthesia. He stated that the anesthetic solution produced "arachnoiditis," an inflammation of the spinal cord which constricts and damages the nerves and which occurs as the result of an unusual reaction of the patient to the solution employed in the procedure.

*192 F. 2d 181 (3d Cir. 1951).

Inasmuch as expert testimony ascribed the injury to the toxic quality of the injected drug as distinguished from negligence of the anesthesiologist, that evidence was binding on the court. No expert testimony pointing up possible negligence of the physician was introduced; hence the jury was not permitted to speculate as to the cause and the case was withdrawn from their consideration. Judgment followed for the defendants, and the plaintiff appealed to the United States Court of Appeals where judgment for the defendant physicians was affirmed.

This case only reiterates a long-standing rule of malpractice litigation, that the plaintiff must prove his proposition by expert medical testimony for the reason that a jury of laymen cannot have a valid opinion on complex medical questions unless furnished that opinion by physicians testifying as experts in the case. When expert testimony is not produced, the case is withdrawn from the jury and judgment is entered for the defendant physician as a matter of law.

It goes without saying that expert testimony is not required in every case, for under certain circumstances negligence charged may involve matters of such general knowledge that the jury is competent to draw its own conclusions without benefit of technical assistance. These include instances where surgical sponges and instruments are left in the abdominal cavity; where a drain in an incision is allowed to remain for a period beyond its usefulness; where the wrong tooth is pulled; where the wrong leg is amputated. But in the Ayers case, injury to healthy tissue within the region of treatment constituted an occurrence beyond the layman's imagination and experience. The issue of negligence or no negligence of necessity had to be determined on the basis of expert testimony presented at trial.

Huber vs. Protestant Deaconess Hospital of Evansville†

This case was filed in the Circuit Court of Warrick County, Indiana. The complaint

†133 N.E. 2d 864 (Ind. App. 1956).

(Continued on page A-40)

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charged the defendant anesthesiologist with negligence in administering anesthesia in connection with an operation for the removal of the plaintiff's appendix. Dr. McDonald, the surgeon, and the Deaconess Hospital Association were joined as defendants. Among the various allegations were charges that the injection was too high, too deep and at the wrong angle, that the wrong solution was used with the wrong instrument, and that the instrument was injected improperly. There was conflicting evidence as to where the spinal anesthetic was administered, but Dr. Tilden, the anesthesiologist, testified that the needle should be inserted between the second and third lumbar vertebrae.

The patient's parents testified that after the operation they noticed a red spot on the patient's back, to the left of the spine and a short distance below his shoulder blade. A physician who examined the patient testified that the patient pointed to a place in the region of the twelfth thoracic vertebra as the spot where the injection was made. There was additional medical testimony that the plaintiff had sustained a partial conus injury which could be produced only in the spinal cord and could not be produced in the sacral and lumbar nerves of the lower equina.

On the basis of evidence received, the trial court directed the verdict against the plaintiff and for all defendants. On appeal to the Appellate Court of Indiana, that court reversed the judgment as to Dr. Tilden, the anesthesiologist. Considering all the evidence, the Appellate Court found that there was substantial basis for a reasonable inference that an ulterior act, contrary to the usual and accepted standards of reasonable care and constituting actionable negligence, was committed by Dr. Tilden. Due to the fact that the anesthesiologist was supplied by the hospital, that she had a good reputation and was an experienced, qualified specialist, the surgeon was justified in relying on her reputation for competence and was in no sense negligent. Furthermore, the surgeon was in another room at the time the anesthetic was administered, and no one would assume that it was being administered under his direction and control.

Since the anesthesiologist, as a physician, was considered to be an independent contractor, thus not an agent of the hospital, the hospital was liable only to the extent that it may not have used due care in employing her in the first instance. But due care was used in employing a reasonably competent, licensed physician. The Appellate Court also pointed out that under Indiana law it was unlawful for a corporation to practice medicine, indicating that the right to practice medicine was strictly a personal privilege which could in no sense be delegated.

*Cavero vs. Franklin General Benevolent Society**

This was an action for the wrongful death of the plaintiff's minor son during a tonsillectomy. There was expert testimony to the effect that the nurse anesthetist gave too much ether to the patient. One of the surgeons noted that the patient's blood was unusually dark and further noted that the anesthetist was charged with the duty of watching the blood, its flow and color. Failing to recognize signs of respiration, the surgeon immediately instituted artificial respiration and called for a mechanical resuscitator. The resuscitator was not in the room and the anesthetist left the room, returning with the machine three or four minutes later. The resuscitator was used but failed to revive the child, and experts were of the opinion that the child had died by the time the machine was brought into the room, death resulting from the administration of an overdosage of ether.

Verdict was for the plaintiff in Superior Court, the jury finding that the nurse was negligent because of her lack of vigilance. Since she was an employee of the hospital, the institution was held liable under the doctrine of *respondeat superior*. On appeal to the Supreme Court of California, judgment for the plaintiff was affirmed. There was, of course, no sound reason for predicating liability on the part of the surgeon, as he was in no way responsible for the administration and regula-

*223 P. 2d 471 (Calif. 1950).

(Continued on page A-42)

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tion of the anesthetic nor did he exert control over the activities of the anesthetist. It is possible that a surgeon may insist on supervising anesthesia, in which case he might be considered in control and liable if the hospital employee is negligent. The final test in any case must depend on the practices or routine medical customs followed in a specific community or hospital.

Woodson vs. Huey*

This case originated in the District Court of Tulsa County, Oklahoma. Esther Huey retained Dr. Carney to perform an appendectomy. Dr. Carney recommended Dr. Woodson as anesthesiologist and the patient acquiesced in his recommendation. Answering the patient's inquiry with regard to choice of anesthesia, Dr. Carney suggested spinal anesthesia, but the patient immediately informed him of her fear of spinal injections and specifically requested him not to proceed with spinal anesthesia.

In the hospital prior to operation, the patient asked a nurse if she was going to receive a general anesthetic and the nurse informed her that since she was Dr. Carney's patient she would most likely receive a spinal anesthetic. She asked the nurse to call Dr. Carney and inform him of her desires not to submit to spinal anesthesia, but the nurse refused, complaining that she was too busy. She asked the nurse to call Mr. Huey, but the nurse reiterated that she was too busy to call anyone. Without doubt, the intransigence and cold demeanor of the nurse aroused ire which was transferred to the physicians who were involved in the case.

On the morning of operation the patient was given the usual sedation and taken to the operating room. She was hazy and groggy, and Dr. Carney was not present when she arrived in the operating room. The surgical nurse told her to turn over on her right side, which she did. Very shortly thereafter she experienced a sharp pain which coursed through her legs to her feet.

Dr. Carney, the surgeon, testified that he instructed the hospital staff to place a definite notation on her chart, "No spinal anesthesia," and insisted that the notation was made. By the time he entered the operating room, the patient had already received her spinal injection. Dr. Woodson, the anesthesiologist, testified that he examined the patient's chart and found nothing to indicate that it would be dangerous or improper to employ spinal anesthesia. He testified that he told the patient it was a safe anesthetic and that the patient replied: "Well, I will not be obstinate, but I want to go to sleep." He asserted that he introduced the spinal needle into plaintiff's fourth interspace and injected the anesthetic, that he injected PENTOTHAL® sodium into her arm, and that immediately thereafter she went to sleep.

An expert witness called by the plaintiff testified that on the basis of examination of the plaintiff and of her hospital records, it was his opinion that the plaintiff had sustained a puncturing of the spinal cord by something introduced into the cord which had resulted in active inflammation of the spinal cord. In his opinion the puncture was made in the fourth lumbar interspace.

A judgment against both physicians in District Court was reversed as to Dr. Carney by the Supreme Court of Oklahoma. The Supreme Court ruled that Dr. Carney was not an insurer, that he did everything he could be reasonably expected to do under the circumstances, that Dr. Woodson was not his agent. The court found Dr. Woodson guilty of a technical assault, for lack of consent, express or implied, to administer spinal anesthesia. A finding that the plaintiff had never assented inhered in the jury's verdict.

Written consent is not required by law, though such is desirable in order to avoid the usual misunderstandings leading to litigation. In connection with the written consent to an operation, one paragraph might well be devoted to consent to anesthesia, and this consent should be signed by the patient. If the patient is married, consents should be signed by patient and spouse; in the case of a minor, consents should be signed by both parents or

*261 P. 2d 199 (Okla. 1953).

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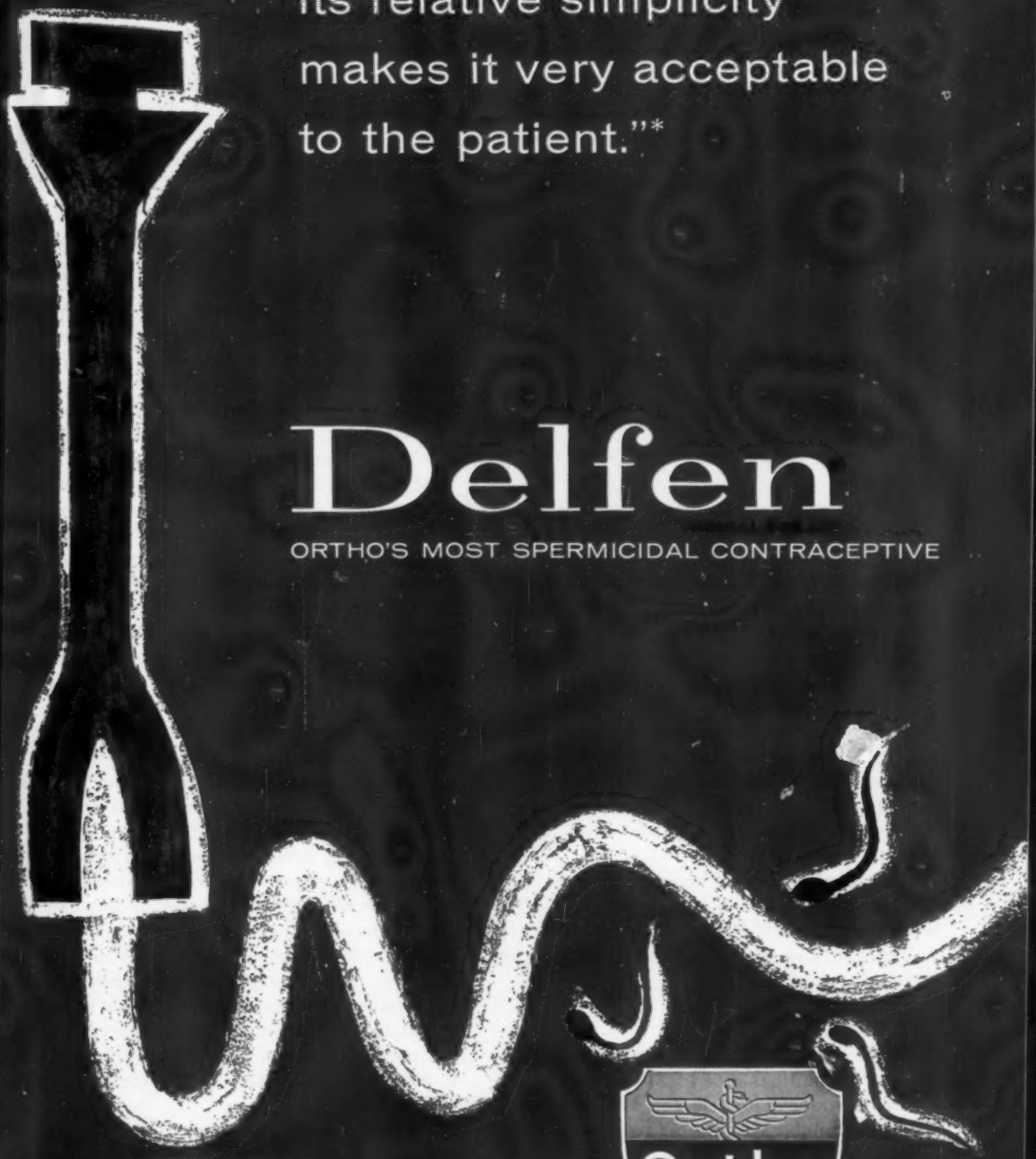

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*Baker, D., Clark, F., Jennings, M., Pollak, V., Glass, H., Wolf, L., and Tyler, E. T.: West. J. Surg. 64:152, 1956.

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by the legal guardian. Anesthesiologists, whenever possible, should consult with their patients prior to surgery, obtain consents and explain procedures. Except where emergency situations dictate otherwise, preoperative consultations will in large measure palliate unreasonable fears and expectations.

Certain factual conditions occurring in malpractice actions may lead to the introduction of the doctrine *res ipsa loquitur*. Stated simply, this is a rule of probabilities peculiar to the law of evidence. It is a qualification of the general rule that negligence is never presumed and must be proved. The following conditions are necessary for the rule to apply: (1) The accident must be of a kind which does not ordinarily occur in the absence of negligence; (2) the situation must be under the control of the defendant, his agent or employee; (3) the accident must not have been due to any voluntary action or contribution on the part of the plaintiff.

In a majority of American jurisdictions, the rule creates an *inference* of negligence on the part of the physician-defendant which the jury will be permitted but not compelled to accept. In a minority of jurisdictions, the rule creates a *presumption* of negligence which requires a directed verdict for the plaintiff if the physician offers no evidence to rebut it.

The rule was originally applied only in obvious cases, where lay testimony could be employed in discerning the presence or absence of negligence. Thus negligence might be inferred where instruments are left within the abdominal cavity or where the wrong leg is amputated.

An examination of recent appellate opinions reveals that the rule has been applied with increasing frequency to anesthesiologists, particularly in cases in which spinal anesthesia is involved.

Seneris vs. Haas*

This case has received widespread comment in medical and legal circles. Jessie Seneris was admitted to the Methodist Hospital of Southern California as a routine obstetric case. The hospital selected defendant Dr. West, one of six staff anesthesiologists, to administer a spinal anesthetic to the patient. The delivery itself was spontaneous and uncomplicated, but in the first days post partum the patient complained of pains in her back, neck, head, arms and wrists. At the time of the trial, the patient was still suffering pain in her left hip and she had only limited use of her left leg.

Mrs. Seneris filed suit against Dr. West, the anesthesiologist, charging negligence; against Dr. Haas, the obstetrician, claiming that he knowingly permitted Dr. West to administer the anesthetic, and against the hospital under the doctrine of *respondeat superior*. A written report by a staff neurologist, contained in a hospital record, noted the presence of sensory loss, motor weakness and reflex change in the left leg, indicating cord damage on the left in the lumbar region. Dr. Haas, the obstetrician, testified that it would be bad practice to inject a needle into a vertebral space above the first lumbar vertebra, that actually in general practice one never goes in above the second lumbar vertebra. He also testified that it was his opinion that the nerve roots were affected by the anesthetic solution and that permanent paralysis should not result when due care was observed and proper practice followed.

Dr. West, the anesthesiologist, unequivocally testified that he inserted the anesthetic solution at the interspace between the fourth and fifth lumbar vertebrae. He stated that he used the standard accepted kind and amount of anesthetic normally employed in obstetric cases, and that there was no contraindication to the use of spinal anesthesia in this case. He did, however, explain that occasional sensitivity to these agents occurs in isolated cases, thus Mrs. Seneris may have been sensitive to the anesthetic solution. He asserted that he had a definite opinion that there was no cord damage present in this case, and that in arriving at this conclusion he had taken several factors into account.

Plaintiff's counsel contended that the evidence circumstantially established the fact

(Continued on page A-46)

*45 Cal. 2d 811, 291 P. 2d 915 (1955).

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that the spinal cord was injured. As part of their case in chief they offered the deposition of one Dr. Webb, relating that the anesthetic needle had been inserted in the area opposite the twelfth thoracic and the first lumbar vertebrae. This evidence was rejected in trial court because of Dr. Webb's lack of qualifications to testify as an expert. A judgment of nonsuit was rendered against the plaintiff by the judge of the Superior Court of Los Angeles County and affirmed in the District Court of Appeal. In the Supreme Court of California, judgment of nonsuit was affirmed as to the obstetrician, Dr. Haas, but reversed as to Dr. West and the hospital.

In reversing, the Supreme Court ruled that it could have been legitimately inferred by the jury that the plaintiff's injuries were proximately caused from spinal cord damage caused by a spinal anesthetic administered between the twelfth thoracic and the first lumbar vertebrae, and ruled further that a spinal anesthetic administered in that location was not good medical practice. The appellate opinion also pointed out that the trial court had abused its discretion in rejecting the deposition of Dr. Webb, thus denying the plaintiff a fair opportunity to prove her case.

Notwithstanding the fact that the Supreme Court concluded that plaintiff's evidence was sufficient to present a prima-facie case, it concluded by way of dictum that the doctrine of *res ipsa loquitur* could be applied in the instant case. This would mean, then, that the jury should be permitted to determine whether or not each of the conditions of the rule was present.

It should be remembered that the doctrine at the very least creates an inference of negligence on the part of the defendant physician, and the doctrine is applied here to a situation which most certainly involves a calculated risk. It is true that an injury does not ordinarily occur in cases of this type, but it does not follow that lack of due care is more probable than not when injury does occur. If it could be said that a negligent cause was more probable than a non-negligent cause, the doctrine might well apply; but this obviously was not the case in the instant fact situation.

Simply because an accident does not ordinarily occur in the absence of negligence, one should not jump to the erroneous conclusion that negligence is the more probable cause. There is, indeed, a possibility of negligence, but there is no showing of strong probabilities. On the basis of this theorizing, however, one should not infer that the doctrine should be forever barred from consideration in malpractice litigation. One must be aware that the task of proving a prima-facie case is often a very difficult and frustrating experience. The unwillingness of members of the medical profession to testify against one another may impose a tremendous handicap on the plaintiff in cases where negligence is obvious to the discriminating eye but where real expert proof is lacking. The courts insist on expert testimony; it may for practical purposes be unavailable.

It is to be regretted that the pull and haul of materialism have exerted such a profound influence on the procedures of malpractice litigation. Given the combination of grasping, ambitious lawyers and suspicious, recalcitrant physicians, there is scant reason to believe that matters will augur well for the general public. Solutions are not immediate, yet attempts are being made to correct the ills of interprofessional rivalry. Professional associations in New York, Los Angeles and Cincinnati, among others, have accomplished significant results in terms of invoking enthusiasm for cooperative appraisal of the many inadequacies of the present system. To effect substantial improvement, these basic postulates must be accepted: (1) Flimsy, if not fraudulent, claims must be rejected; (2) a gentleman's agreement should be drafted, providing for satisfactory communication between lawyers and physicians with respect to adequate preparation of medical evidence; (3) medical associations should be held to the task of providing expert medical witnesses who will relate medical facts as they see them, without hint of partisan distortion. In the summing up, any system that compels ascertainment of the truth is worth striving for. When one countenances dishonesty, he courts dissatisfaction—in any case.

Radiology FOR PRACTICING PHYSICIANS

Fibrous Dysplasia of Bone

PAUL C. HODGES*

In the year 1891, Friedrich von Recklinghausen, at that time professor of pathology at the University of Strasbourg, contributed to a *festschrift* for Virchow a monograph dealing with a group of skeletal diseases, including fibrosing or deforming osteitis, osteomalacia and osteoplastic neoplasm.[1] Three of his cases (Nos. 5, 6 and 7) were characterized by more or less generalized fibrous osteitis, a condition which he called "osteitis fibrosa cystica generalisata," and which presently is known also as "Von Recklinghausen's disease." Snapper[2] paraphrased Von Recklinghausen's findings as follows: "The skeleton had become soft. The bones were bent and spontaneous fractures had occurred. At autopsy the bones were friable and deformed. The skeleton had the consistency of decaying wood and the cortex of the bone could be cut with a knife. Not one bone of the whole skeleton had escaped this decalcifying process, which was, in the true sense of the word, generalized. On histologic examination, the bone substance was replaced by hard fibrous tissue. In the tibia, the iliac crests, the lower and upper jaws of his patients, bone cysts and brown tumors were found, the latter consisting of rapidly proliferating giant cells."

For two reasons this famous 1891 monograph eventually came to be both a landmark and a mirage for students of skeletal disease. Von Recklinghausen was already the eponym for multiple fibromatosis,[3] a disease that was known to involve the skeleton along with other tissues; now, there was a second and presumably different Von Recklinghausen's disease. In 1926, Mandl, at Erdheim's suggestion,[4] cured a case of Von Recklinghausen's disease of bone by finding and removing a parathyroid adenoma; however, it subsequently became clear that not all patients with skeletal lesions similar to those described by Von Recklinghausen had parathyroid hyperfunction.

In the past two decades, through the work of Albright and associates,[5] Lichtenstein[6] and Kornblum,[7] the term "fibrous dysplasia" has

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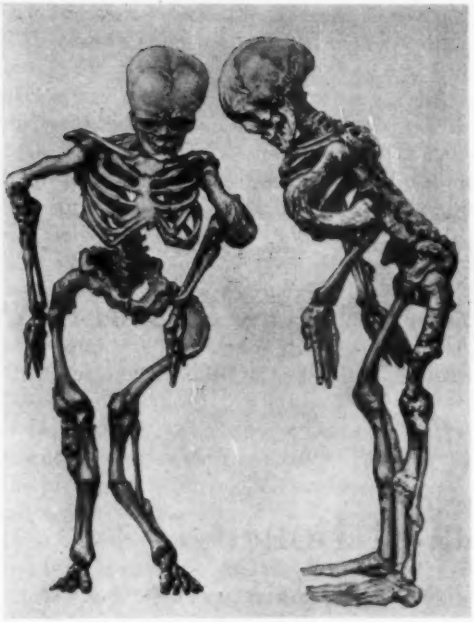


FIGURE 1. Skeleton of patient with osteitis fibrosa cystica generalisata. Reproduced from case 6 of Von Recklinghausen's monograph.[1]

come into general use. About the best one can say for the term is that most pathologists and clinical workers have come to know what it means, and until we gain some knowledge of the cause of the disease we are not apt to come up with a better term.

Nature of Fibrous Dysplasia

Fibrous dysplasia is a nonmalignant, possibly congenital, skeletal disease which affects women slightly more frequently than men. The more severe cases usually involve the skin as well as the bones. The lesions consist of nonelevated areas of pale brown pigmentation on the trunk, buttocks, thighs or neck, and in some female patients there is sexual precocity. The skeletal lesions may involve a single bone, but they usually are multiple, with a tendency toward unilateralism and a distribution roughly corresponding to the skin lesions when the latter are present.

Unlike hyperparathyroidism, the blood calcium and phosphorus levels are within normal limits; there is no abnormal excretion of calcium in the urine and no generalized loss of calcium and phosphorus from the bones. X-ray examination of the maxillae, therefore, fails to show demineralization of the lamina dura; radiologically and microscopically, the skeleton remains normal except in those regions in which involvement is grossly obvious. Of course, if multiple recurring fractures of the lower extremities lead to enforced inactivity, there will be disuse osteoporosis.

The lesions of fibrous dysplasia are most characteristic when they involve the tubular bones; the femur, tibia, humerus and radius are most frequently affected. Lesions sometimes occur in the vault and the base of the skull, the jaws, pelvis, ribs and spine, and it is doubtful if any part of the skeleton is completely immune. In a typically involved tubular bone—for example, the femur—the lesion may be confined to the proximal third, with the rest of the shaft remaining normal. Within the involved region the shaft is broadened, the cortex thinned, and the normal pattern of substantia spongiosa more or less completely smudged out. When longer segments of the shaft are involved, the trabecular pattern may be altered in some regions and wiped out in others, the regions of total loss being radiologically indistinguishable from cysts. Several of the ablest students of the disease, being convinced that solitary bone cyst and fibrous dysplasia are totally unrelated entities, declaim against the tendency of some radiologists and even some pathologists to refer to these smudged-out areas as cysts. It is true that the x-ray pattern which looks like the boundary zone of a cyst usually turns out to be a mere accidental pattern of old trabeculae or abnormal new bone, but a pathologist as able as Von Recklinghausen did describe cysts in a case now presumed to be fibrous dysplasia. It remains to be shown that fibrous dysplasia never begins as a localized cyst or undergoes cystic degeneration.

When most of the femoral shaft is involved with fibrous dysplasia, there is apt to be characteristic lateral bowing with recurring fractures and with deformity that requires osteotomy. The skull lesions are predominantly

FIGURE 2. Severe generalized fibrous dysplasia in a 16 year old boy. Shepherd's crook deformity of the left femur is similar to that shown in figure 1.

FIGURE 3. Skull of patient shown in figure 2. Unlike the long bones, in which destruction predominates, the skull bones undergo sclerosis and hyperostosis, which usually produce secondary damage to the optic nerve.

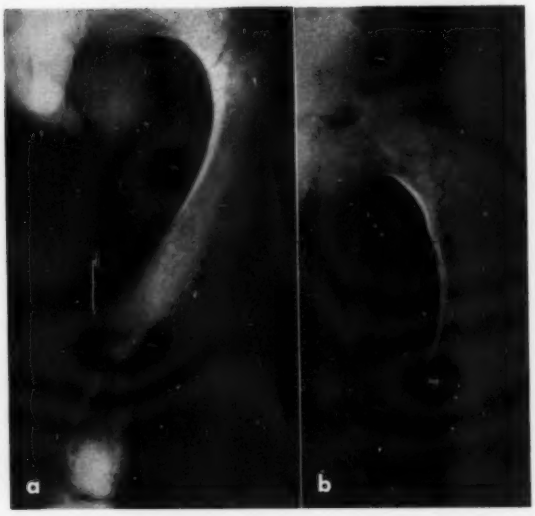


FIGURE 4a. Left femur of the 16 year old boy shown in figure 2. b. Three years later, after surgery had partially corrected the deformity.

FIGURE 5. Skin lesions of fibrous dysplasia in a 26 year old man. The pigmented areas have serrated edges, which Albright likened to a map of the coast of Maine. Distribution of the skin lesions corresponds roughly with that of the underlying skeletal lesions.

FIGURE 6. Lower right ribs of the patient shown in figure 5. In the tenth and twelfth ribs, the cortex is thinned and expanded and the substantia spongiosa lacks normal trabeculation.

FIGURE 7a and b. Lateral view and frontal view of excised rib of patient shown in figure 5. Microscopic examination showed dense fibrous tissue with sparsely scattered thin trabeculae of bone throughout.

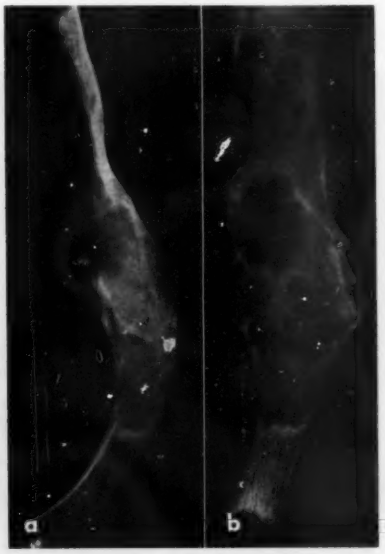


FIGURE 8a. Minimal changes in the right humerus of an 18 year old girl with fibrous dysplasia of the long bones. b. Pathologic fracture, which occurred four years later, due to thinning of the cortex. c. Typical lesions seen in the right tibia and fibula when patient was 20 years old.

FIGURE 9a and b. Frontal view and lateral view of the shaft of the left humerus of a 17 year old girl, showing typical lesions of monostotic fibrous dysplasia. No other bones were involved.

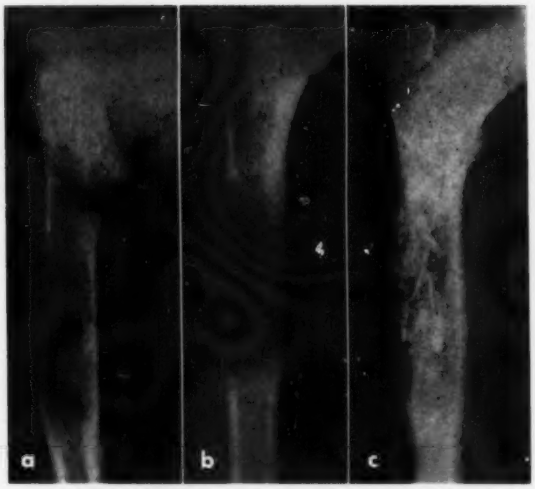


FIGURE 10a and b. Lateral view and frontal view of the shaft of the right femur of a 13 year old girl with regional fibrous dysplasia. The first symptom of the condition was a pathologic fracture, which occurred while the patient was roller skating. c. After surgical curettage of typical fibrous dysplasia tissue had been performed and the cavity filled with bone chips.

FIGURE 11a and b. Frontal view and lateral view of the right tibia and fibula of the patient described in figure 10, showing typical fibrous dysplasia with pathologic fracture. History revealed there had been a previous injury to the right tibia. c. One year after curettage and insertion of bone chips.

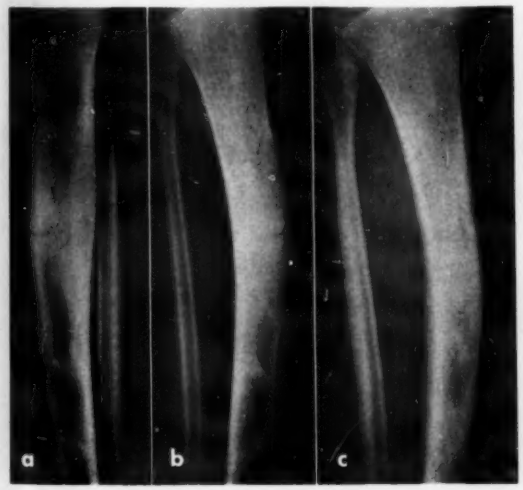
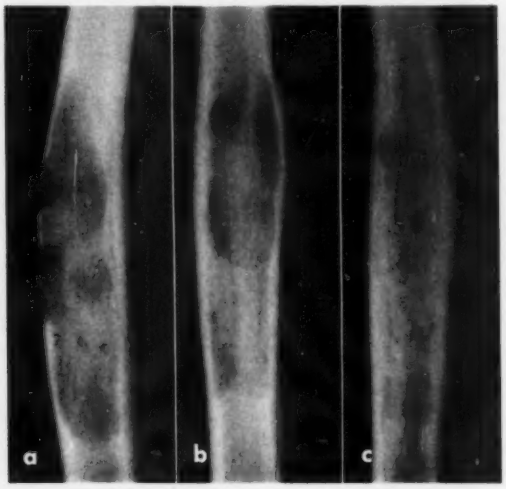


FIGURE 12a and b. Lateral view and frontal view of the femur of a 42 year old woman with monostotic fibrous dysplasia. Part of the cortical defect was caused by preoperative biopsy. At operation, the cortex was thin and the medullary canal was filled with dense fibrous tissue containing cystic areas filled with blood-tinged fluid. c. Nine months following surgery.



osteoplastic, and, when they are progressive and involve the base, damage to the optic nerve and brain may be severe. Fibrous dysplasia of the mandible leads to severe disfigurement, but it sometimes responds well to plastic surgery.

Gross and Microscopic Pathologic Findings

On direct inspection of a typically involved long bone, the surgeon finds the medullary canal grossly dilated and filled with firm, dirty gray fibrous tissue which, on being rubbed between the fingers, feels gritty. Microscopic examination reveals a stroma of white fibrous connective tissue in which there are irregular branching strands of embryonic bone.

Treatment and Prognosis

Surgery is the only known treatment for fibrous dysplasia, and even it is used mainly to manage fractures and to correct deformities. In a few instances, complete extirpation of the abnormal fibrous tissue has seemed to expedite arrest; sometimes, the disease is self-limited. More often, particularly in severe cases, there is slow but progressive deterioration; however, the complication of malignant degeneration, which is seen in Paget's disease, has not been observed.

REFERENCES

1. Von Recklinghausen, F. D.: Die Fibröse oder Deformirende Ostitis die Ostiomalacie und die Osteoplastische Carcinose in Ihren Gegenseitigen Beziehungen. In Festschrift for Rudolf Virchow. Berlin, G. Reimer, 1891.
2. Snapper, I.: Medical Clinics on Bone Diseases. New York, Interscience Publishers, Inc., 1943.
3. Von Recklinghausen, F. D.: Uber die multiplen Fibrome der Haut. Berlin, A. Hirschwald, 1882.
4. Garlock, J. H.: Differential diagnosis of hyperparathyroidism with special reference to polyostotic fibrous dysplasia. Ann. Surg. 108:347-361, 1938.
5. Albright, F., Butler, A. M., Hampton, A. O. and Smith, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females. New England J. Med. 216:727-746, 1937.
6. Lichtenstein, L.: Polyostotic fibrous dysplasia. Arch. Surg. 36:874-878, 1938.
7. Kornblum, K.: Polyostotic fibrous dysplasia. Am. J. Roentgenol. 46:145-159, 1941.

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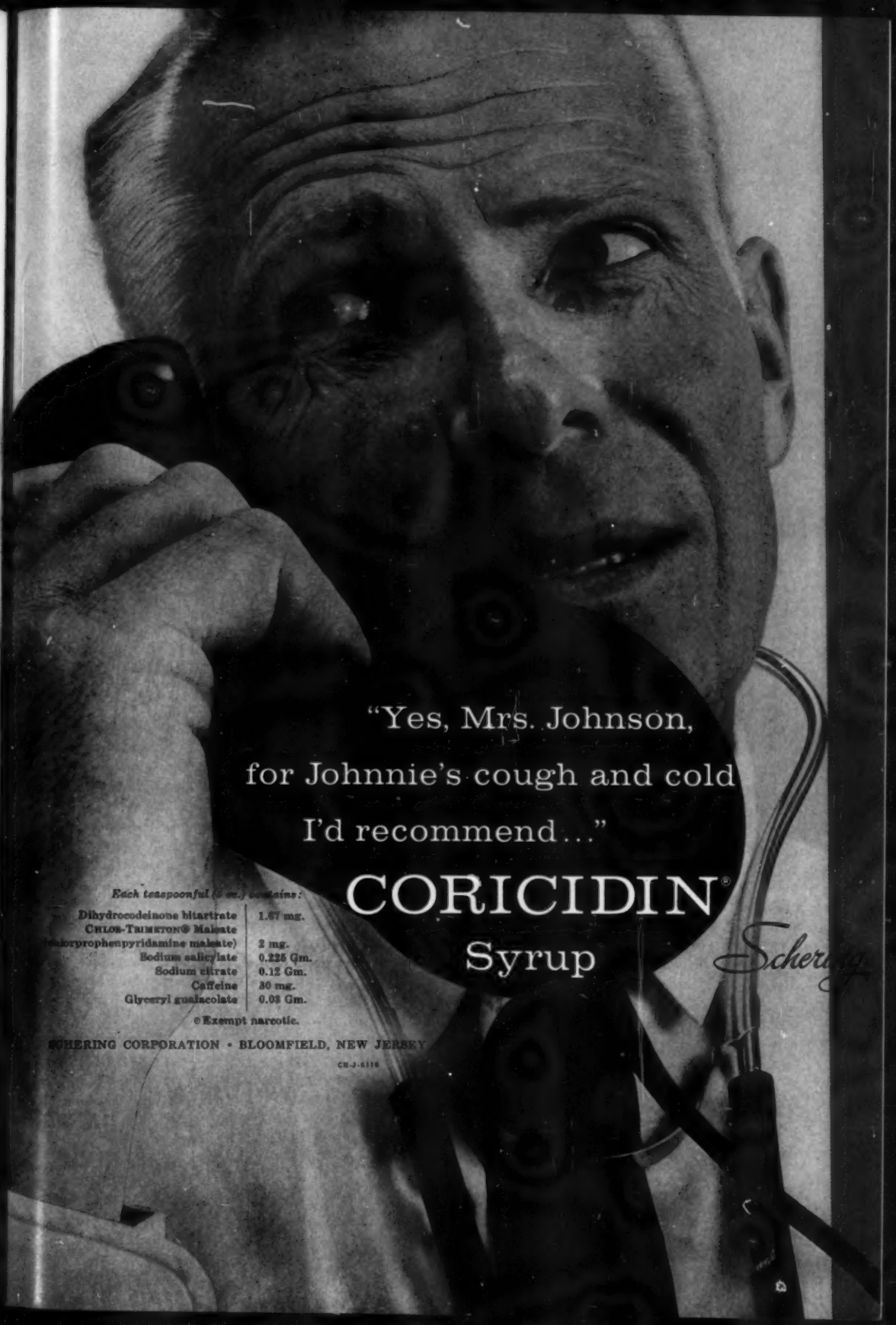
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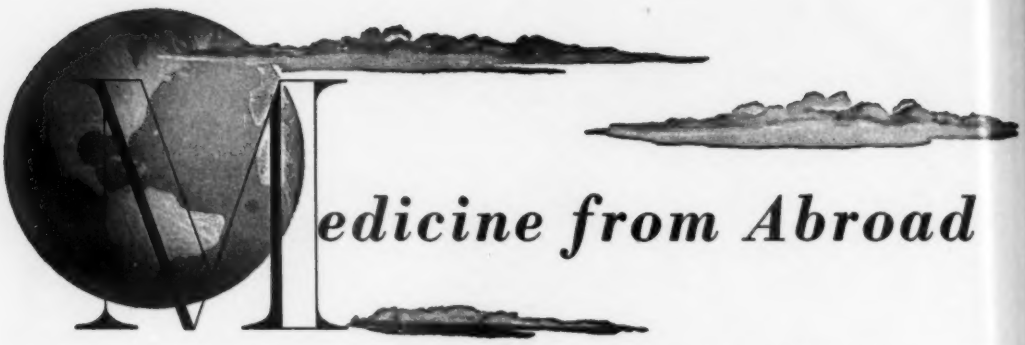

Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Chlorothiazide—In the *Medical Journal of Australia*, Drs. R. J. Marshall and A. J. Barnett, Baker Medical Research Institute, Alfred Hospital, Melbourne, discussed the use of the oral diuretic chlorothiazide in promoting diuresis and in enhancing the antipressor effect of ganglion-blocking drugs in hypertension. Case histories were presented of patients to whom the diuretic was administered with good results and of hypertensive patients who were treated with chlorothiazide and mecamylamine. The authors also reviewed in detail the changes in serum electrolyte levels, particularly those of sodium, potassium, chloride and water.

It was found that the action of chlorothiazide is comparable to that of the parenterally administered organic mercurial preparations, such as mersalyl, and that it potentiates the effect of ganglion-blocking drugs in hypertension. However, before a final evaluation is made, more experience is required in respect to possible toxic effects or to the development of a refractory state after prolonged use. Such effects, however, have not been noted in patients treated for periods of up to three months. The authors concluded that chlorothiazide is of marked pharmacologic interest, has therapeutic possibilities, and will probably prove effective in managing patients with edema.

AUSTRIA

Complications following hysterectomy—J. Froewis and H. Kremer reported to the Austrian Society for Gynecology and Obstetrics on prolapse of the bladder and urinary incontinence following hysterectomy. Some of the 1,053 patients studied were operated on through the vagina; others had a laparotomy. Age, occupation and parity of the patients were considered, as well as whether prolapse had been noticed before or after the operation.

Results of the study indicated that removal of the uterus by the Viennese technic was not perceptibly related to subsequent sinking or prolapse of the bladder, although urinary incontinence increased slightly after hysterectomy in these cases. According to the authors' observations, the woman's occupation was significant in the recurrence of prolapse or incontinence. Aside from the usual colporrhaphy, an additional operation seemed necessary only to prevent recurrence of prolapse.

Involution of the uterus and vagina—At the same meeting, J. Spurny reported that examinations of 150 women six weeks after delivery showed that good condition of the muscular and connective tissues, as evidenced by the levator contractions, the striae and the condition of the breasts, does not necessarily accompany a good involution of the uterus and vagina, and vice versa. The conclusion that the hormonal factor plays the major role in involution of these organs is supported by the development of hyperinvolution in the presence of inferior mesodermal constitution and by the occurrence of prolapse despite excellent contractility of the levator muscle. This study also contributes to the etiology of prolapse, since it shows the decisive role played by involution.

(Continued on page A-68)

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References:

1. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology 8:504, Dec. 1957.
2. Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.
3. Eskwith, I. S.: The holistic approach to angina pectoris. Am. Heart J. 55:621, April 1958.

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BRAZIL

Roentgenographic studies in pulmonary hypertension—In an analysis of the roentgenographic and angiocardiographic features of pulmonary hypertension, published in *Revista paulista de medicina*, F. Toshiyasu and M. F. Lion found variations of pulmonary vascularization in different stages of the condition. In the early phase, there was slight or moderate vascularization with uniform and proportional decrease of the diameter of the vascular tree from the hilus to the periphery. In the intermediate period, the vascular tree became accentuated and the hilus was enlarged; angiocardiography revealed a delay in the progress of the contrast medium. In the late stages, pulmonary vascularization in the periphery was poor and the hilus was greatly enlarged. During this stage, the emptying of the contrast medium from the pulmonary tree was noticeably slow.

Varied degrees of right ventricular hypertrophy corresponding to the different stages of the disease were observed. Right ventricular hypertrophy increased as the organic pulmonary vascular alterations resulting from marked pulmonary hypertension became more accentuated. The authors emphasized the importance of the clockwise rotation of the heart in the longitudinal axis for evaluating the size of the cardiac chambers and the modification caused by the left ventricle, which may or may not be overstrained.

After analyzing the relation between the middle arch, the pulmonary artery and right ventricular hypertrophy, these investigators reported on the roentgenographic and angiocardiographic features of the following conditions: primary pulmonary hypertension; congenital cardiopathies affecting the transmission of pressure and blood from the systemic circulation to the pulmonary vascular bed; chronic pneumonopathies such as emphysema; and acquired and congenital pulmonary angiopathies, such as schistosomiasis, thrombosis, embolism and, particularly, sickle cell anemia. In these diseases pulmonary hypertension is accompanied by normal pulmonary capillary pressure. The diseases in which capillary pressure is elevated either by mitral stenosis and pericarditis or by left ventricular failure were also discussed.

Laryngocele—In *Revista paulista de medicina*, N. A. Cruz and J. B. Fairbanks reported on two cases of laryngocele associated with cancer of the larynx and one case in which the laryngocele was primary, bilateral and external. On reviewing the literature and their own cases, the authors concluded that primary laryngoceles are rare; however, laryngoceles secondary to laryngeal carcinoma may be present but often remain undetected. Laryngoceles were found in only two (1.6 per cent) of 120 cases of confirmed cancer of the larynx. Roentgenographic examination of patients with cancer of the larynx may reveal laryngoceles which were missed clinically. Tumors of the ventricles and of the false cords produce optimal conditions for the development of secondary laryngoceles. Two of the cases cited illustrated the relationship of laryngocele to cancer of the larynx involving the ventricles or ventricular bands, as reported by Cova and Meda.

ENGLAND

Advances in treatment—In the annual review of advances in treatment in the *Practitioner*, Dr. Bodley Scott, St. Bartholomew's Hospital, discussed the corticosteroids, diuretics and hypotensive drugs. He concluded that none of the drugs described constitutes a cure for any of the diseases in which it is used; relief of symptoms is the aim in all instances. These drugs also illustrate the increasing debt that the medical profession owes to the pharmaceutical chemists. "While we are pleased to acknowledge our indebtedness," he said, "at times we cannot but be overwhelmed by the torrent of powerful preparations with which we are deluged, for they appear with such rapidity that clinical trials are sometimes inadequate."

Dr. Scott observed that there has been little change in the detailed application of the steroid hormones cortisone and cortisol (hydrocortisone) to treatment. The corticosteroids fulfill their physiologic function in the control of Addison's disease. The place of corticosteroids in the treatment of rheumatoid arthritis is still debatable. In the collagen diseases—polyarteritis nodosa and disseminated lupus erythematosus—no other agents have any therapeutic effect, with the possible exception of chloroquine in the latter disease; there is, therefore, no alternative to their use.

(Continued on page A-71)

Until recent years the mercurials have been indisputably pre-eminent among the diuretics, but several competitors have now appeared. The first of these, acetazolamide (DIAMOX®) was shown to be a powerful inhibitor of carbonic anhydrase, but in practical therapeutics it proved disappointing, and it cannot rank with the mercurials. Another group of diuretic drugs is the amino-uracil series, of which amisometradine (ROLICTON®) has been subjected to clinical trial. It caused less frequent and less severe gastrointestinal symptoms, but had only 40 per cent of the diuretic activity of 2 ml. mersalyl. A more serious rival to the mercurials is chlorothiazide (SALURIC®), the action of which depends on an enhanced secretion of chloride with an equimolar loss of sodium. It has been shown to be an efficient diuretic devoid of toxic effects.

During the past 10 years a succession of drugs which lower the arterial pressure has been introduced. Those most widely employed have been the ganglion-blocking agents, but almost all these have had undesirable side effects on the alimentary tract. Moreover, many have shown vagaries of absorption that have made their use hazardous. Two members of a new group of ganglion-blocking substances have recently been submitted to clinical trial and appear to be promising. The first of these is pentacynium methylsulfate (PRESIDAL®); after oral administration of this drug, reduction of blood pressure starts in 20 to 30 minutes and is maximal in one hour. Treatment is started with the oral administration of 50 mg. three times daily; the dose is increased by 25 mg. at intervals of two days until the desired effect is obtained. Side effects are mild and their severity decreases with continued use of the drug. Another recently introduced ganglion-blocking drug is pempidine (PEROLYSEN® or TENORMAL®), a tertiary amine freely absorbed from the gastrointestinal tract. After a single orally administered dose the hypotensive effect begins in two to four hours, is maximal after another one to three hours, and terminates after six to seven hours.

Ulcerative colitis in children—At a meeting of the section of pediatrics of the Royal Society of Medicine, Dr. B. Schlesinger and Dr. J. Platt, Great Ormond Street Hospital for Sick Children, London, discussed ulcerative colitis in childhood. Their findings in a follow-up study of 60 children seen between 1938 and 1956 showed that the illness in childhood did not carry such a discouraging prognosis as was generally supposed. Rectal hemorrhage was the only initial symptom in 17 per cent of the patients; an additional 27 per cent had abdominal pain or constitutional disturbance for weeks or months before the stools became frequent or abnormal.

Although there was a disturbed family background or some calamity prior to the onset of symptoms in one-third of the patients, two-thirds of the children seemed to enjoy a happy, stable home. Nevertheless, the children did tend to show certain characteristics, particularly, undue conscientiousness, with concern over school performance and fastidious cleanliness. Frequently they seemed unduly dependent on or at odds with one parent—usually the mother. They had difficulty in expressing their emotions by word or action, and emotional crises were manifested by a relapse of their colitis. Almost one-fourth the children were Jewish; this was four times the average number of Jewish children found among the total admissions to the Hospital for Sick Children. There was a family history of ulcerative colitis in 17 per cent of the close relatives of patients in the series, including two brothers and a brother and sister. The incidence was greater than in other published figures.

On examination the children were notably above average in intelligence and below average in weight. Tachycardia was the only other striking physical sign apart from the appearance of the stools. Sigmoidoscopic and barium enema studies were incomplete. However, they affirmed that although the rectum and sigmoid colon were occasionally spared it was common to find granular proctitis in the absence of x-ray changes. The disease could spread later to involve the entire colon. The ileum was demonstrably affected in three patients. The usual complications had occurred, and the presence of arthritis in 20 per cent of cases was emphasized. It differed from rheumatoid arthritis in its distribution and course.

It is important to realize that 55 per cent of the patients were well 10 years after the start of their symptoms, even though a few had had protracted or severe illness during childhood. Unless the disease could not be controlled by medical treatment, there seemed to be no indication for surgery until the patient was 14 or 15 years of age. Thereafter, symptoms, if still present, would persist; or the child would die unless colectomy, preferably with ileorectal anastomosis, was undertaken.

Eisenmenger's syndrome—Eisenmenger's syndrome may be defined as pulmonary hyper-

(Continued on page A-72)

tension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at the aortopulmonary, ventricular or atrial level. It may be caused by patent ductus, aortopulmonary septal defect, persistent truncus, transposition with ventricular septal defect, corrected transposition with ventricular septal defect, ventricular septal defect, single ventricle, common atrioventricular canal, persistent ostium primum, atrial septal defect, single atrium, or hemianomalous or total anomalous pulmonary venous drainage into the right side of the heart.

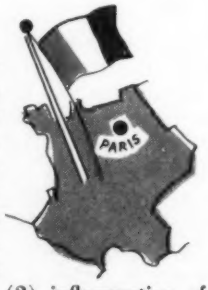
These conditions have in common a large communication between the two circulations, exceeding 0.7 cm. in diameter when aortopulmonary, 1.5 cm. when interventricular, and 3 cm. when interatrial. If the pulmonary vascular resistance were normal, such defects would cause a pulmonary-to-systemic flow ratio of at least three to five, and the usual range would be four to six.

In the *British Medical Journal*, Dr. Paul Wood, National Heart Hospital, London, analyzed 127 cases of the Eisenmenger syndrome. He also studied 53 necropsies of patients well investigated during life. When the shunt was aortopulmonary or interventricular the Eisenmenger reaction was initiated and maintained from birth in at least 80 per cent of the patients; when the shunt was interatrial the reaction was chiefly acquired in 90 per cent. The key to the physiopathology of Eisenmenger's syndrome lies in the behavior and structure of pulmonary circulation in the fetus, in the newborn infant, and also during the first three months of infancy. The fantastic resistance of the fetal pulmonary circulation is attributed to the contorted state of the vessels in fully collapsed lungs. The thick muscular arteries of the fetus and newborn infant represent a functional and structural reaction to high pressure. Expansion of the lung after birth unfurls the pulmonary vessels and lowers the resistance precipitously to around systemic level (about 100 units).

In Eisenmenger's syndrome with aortopulmonary or interventricular shunt, this favorable cycle is prevented by a powerful hyperkinetic factor which maintains the pulmonary artery pressure at systemic level. So long as pulmonary hypertension is maintained, vasoconstrictor tone is not inhibited and the muscular pulmonary arteries do not involute. Obliterative pulmonary vascular disease due to reactive endarteritis fibrosa is secondary and it is rarely observed in infancy.

Medical treatment aims at preventing secondary thrombo-obstructive lesions by use of such permanent anticoagulants as phenindione (DINDEVAN®). Pulmonary vasodilators, such as tolazoline, aminophylline and reserpine, fail to lower the pulmonary vascular resistance and do not influence the course of the disease. Small venesections, repeated from time to time, may be helpful in patients with gross polycythemia, but should be undertaken very slowly and with the utmost vigilance. In recent years surgical repair of the defect in the Eisenmenger syndrome has been responsible for more deaths than has any other cause except hemoptysis. Direct repair of a defect is justified only when it can be predicted with confidence that its closure will result in a fall of pulmonary blood pressure because a hyperkinetic factor of sufficient magnitude will have been eliminated. In practice this prediction can be made when the pulmonary blood flow is at least twice the systemic flow at rest, and the pulmonary vascular resistance does not exceed 10 units. No patient with a pulmonary blood flow less than 1.75 times the systemic flow or with a resistance over 12 units should have the defect repaired in the ordinary way, whether the shunt is reversed, direct or bidirectional. This rule has been observed since its introduction on theoretical grounds in 1950; there have been no deaths from this type of patent ductus since that time.

FRANCE



Subcutaneous inflammations of the leg—In a report to the French Society of Dermatology in Nantes, Professor Bureau distinguished four types of subcutaneous inflammation of the leg: (1) conditions associated with inflammation of the perivascular tissue; (2) inflammation of the vessels (thrombophlebitis); (3) true subcutaneous inflammation (panniculitis); and (4) inflammation accompanied by degeneration or by deposits of such substances as lipid, calcium, etc. Only the first-named type has been thoroughly studied. It was originally described by Bazin in 1861 and was named erythema induratum (Bazin's disease) by Fox and Hutchinson in 1893.

(Continued on page A-74)

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1. Crumpacker, E. L., et al., AMA Arch. Int. Med., 98:314.
2. Palmer, E. D., "Clinical Gastroenterology" Hoeber-Harper.

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True nodular vasculitis, with or without varicose veins, has been described by American and British authors and most commonly affects women between 30 and 60 years of age. It occurs as disseminated nodules (Darier-Roussy sarcoid), as a migrating serpiginous lesion (described by Vilanova), or as a centrifugally expanding inflammation (Bäfverstedt's type).

Histologically, vasculitis involves the arteries and, to a lesser extent, the veins and small vessels. Inflammation of the perivascular tissue with foci of panniculitis occurs where cellular infiltrations overrun and cause the lobules of subcutaneous fatty tissue to atrophy, thereby producing necrotic or necrobiotic areas without ulceration. Streptococci and other pathogenic bacteria are present, but there is no sign of Koch's bacillus.

The other symptoms of Bazin's disease are (1) endocrine disturbances, characteristic of both forms of the disease; (2) circulatory disturbances, chiefly stasis with or without varicose veins but always with cyanosis of the legs; and (3) bacterial allergy. Patients with tuberculosis indurativa are chiefly allergic to tuberculin; patients with nodular vasculitis have multibacterial allergies which can be detected by intradermal reactions to bacterial vaccines. The dominant bacterium is *Streptococcus*, but the allergy is frequently complicated. The amount of antistreptococcin in the blood serum and the presence of infection in the tonsils or elsewhere brings the streptococcal bacteria to the foreground. The sulfonamides also may produce allergic reactions, e.g., indurative subacute erythema following the therapeutic use of sulfadiazine. The presence of vascular lesions perhaps can be explained by the toxic power of blood serum on the capillaries, a theory advanced by Jean Bernard.

No general study has been made of the treatment of these conditions. Therapy must be modified for each patient. It is generally agreed that the new medications are ineffective against Koch's bacillus, and that better results are obtained with Old tuberculin and tuberculosis antigens (such as those produced by Boquet-Nègre of the Pasteur Institute in Paris) supplemented by vitamin D and calcium given intravenously.

Antibiotics such as streptomycin and chloramphenicol, supplemented by cortisone derivatives, are most effective against streptococcal infections. Grupper recommends arterial injections of antistreptococcic vaccine, according to Debray's method of treating rheumatic fever. Thiers of Lyons employs sulfathiourea. It is generally agreed that hormones should be used according to the patient's needs, and that a wide range of adequate measures is available for local therapy.

NETHERLANDS

Hansen's disease—The identity of the leprosy mentioned in the Old Testament and Hansen's disease is disputed by many dermatologists. Dr. K. P. C. A. Gramberg, a physician on Java for many years, asks that the word "leprosy" be abolished from both translations of the Bible and medical literature. He believes that there is no rational excuse for the excessive fear of Hansen's disease, which causes patients to be ostracized from society, dismissed from their jobs, and even to attempt suicide. Hansen's disease is a chronic condition which may be responsive to treatment with modern chemotherapeutic agents. It is contagious only through repeated intimate contact.

The explanation for the fear inspired by the disease may be found in history, particularly, in the Bible. In Leviticus 13 and 14, a disease is described called zara'ath, believed to have been sent from heaven to punish those who disobeyed God's laws. The symptoms were tumors of white skin, with white hairs and a center lying below the surface of the healthy skin; in the course of two weeks the white spots either increased in size or disappeared. An ulcer sometimes formed in the spots, in which case the patient was impure; when the ulcer healed and white spots appeared over the whole body, the patient was pure. This disease was cured by bathing in the water of the Jordan River, which contains sulfur. Anesthetic spots, paresis of the extremities, mutilations, and hoarseness are not mentioned in the Bible. In Greek translations the word "zara'ath" was replaced by "lepra," which Hippocrates described

(Continued on page A-76)

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as a scaly, itching, curable disease of the skin.

From these descriptions it seems highly improbable that zara'ath or lepra is identical with Hansen's disease. In order to abolish the stigma still attached to the disease, which often keeps patients from consulting a physician until the condition is far advanced, Dr. Gramberg suggests leaving the word zara'ath untranslated and substituting the terms "leontiasis" and "leontide" when referring to leprosy or Hansen's disease.

Deaths due to traffic accidents—A survey of the mortality from traffic accidents from 1949 to 1957 has been reported by Bea J. van den Berg and J. H. de Haas in the *Maandschrift voor kindergeneeskunde*. Using data from the central statistical office, the authors found that the mortality rose in this period from 9.6 to 16.5 deaths per 100,000 persons, an increase of 70 per cent.

Motor vehicles were involved in 90 per cent of all accidents. The authors found that the increase in the number of motor vehicles during the period studied was proportional to the increase in mortality.

The age of those killed in accidents varied with the type of vehicle involved. Thirty per cent were pedestrians, the majority being either less than 15 or more than 65 years old. The majority of motor bicyclists killed were from 50 to 64 years old, while young adults comprised the greater number killed in automobile accidents.

In an attempt to improve this situation, school children 11 years of age and older are being taught the principles of safety; however, the authors believe that these lessons would be more effective if started at a much earlier age. Although an enforced speed limit of 50 km. per hour in towns and villages promises encouraging results, it is too soon to draw definite conclusions.

SPAIN

Ophthalmology at the Barraquer Institute—New technics for inducing anesthesia, especially as applied to eye surgery, now permit ophthalmologists to operate for longer periods than was formerly possible. This is especially true when curare is used in addition to local anesthetic agents to effect a temporary paralysis of the eye muscles.

An inaugural address by Dr. Joaquín Barraquer opened the Institute's current course in which 17 American ophthalmologists are participating. One of the principal features of the course is the technic followed in the Institute's new operating theater. The theater is arranged so that the surgeon sits with his back to a transparent half dome; on the other side are seated the specialists and students. The operation is performed about 3 ft. from the observers. The patient, already anesthetized and with eye muscles paralyzed, is brought in on a mobile operating table and is placed with his head turned toward the surgeon. Several devices to aid in the operation are mounted on a mechanical arm suspended above the patient. These include a strong light to illuminate the operating field, a binocular microscope to assist in delicate procedures such as suturing a transplanted cornea, and a television camera used for closed-circuit televising of the operation.

Poliomyelitis—A summary of the poliomyelitis situation in Spain was given by Dr. Bosch-Marin, head of the Spanish puericulture program, at the fifth European Poliomyelitis Symposium, Madrid. He reported that the incidence of poliomyelitis is increasing slightly in Spain. The infant mortality from the disease is 46 in every 1000 births; 91.5 per cent of poliomyelitis cases occur in children from one to five years old.

Thus far only 200,000 persons have been vaccinated against poliomyelitis, but a campaign is under way for mass vaccination according to territorial areas and age groups. The number of children receiving the vaccine is far from adequate, since in Spain there are seven million children less than 15 years of age. An effective immunization program with the Salk vaccine would require 1400 million pesetas a year, but researchers hope to develop a less expensive vaccine. Three researchers, Drs. Sabin, Coprowki and Cox, are working on an orally administered vaccine containing weak live virus, which, if proved effective, would greatly reduce the high cost of immunization.

Hospitalization centers for children who have poliomyelitis have been established in Madrid, Barcelona, Santander and Granada, and one for adults is located in the Hospital del Rey, Madrid; 125 artificial lungs are distributed among 70 cities. A national rehabilitation program for patients paralyzed from poliomyelitis has been organized and is presently being carried out in three hospitals.

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Through the Stethoscope

NOAH D. FABRICANT

When American Doctors Studied Abroad

In the interim between two World Wars, thousands of American doctors went abroad for postgraduate study. Well-organized postgraduate facilities were lacking then, and many tried to find in a foreign country the training their own country failed to give them. Today, the tide of medical migration has been clearly reversed. Thousands of young physicians from all over the world now seek instruction and training in American medical methods and procedures—and get it.

In the 1920s and early 1930s, American doctors undertook postgraduate work in various European centers, Berlin, Hamburg, Rome, Paris and, notably, Vienna. Vienna offered two great advantages: excellent teachers in every branch of medicine and ample cadaver material. In no other city in the world were cadavers so plentiful. Patients dying at the Allgemeine Krankenhaus, the huge municipal hospital where most medical courses were held for foreign doctors, had to undergo autopsy. The laws requiring autopsies covered perhaps half the total deaths in the city at large.

The Viennese appreciated the need for cadaver work as an essential background for training surgeons and surgical specialists. Adam Politzer, who taught otology to several generations of postgraduate students, advocated at least 50 hours of cadaver instruction before a single operation was permitted on a living patient. Told once that cadavers were difficult to obtain, he remarked, "Well, then practice on the living."

Foreign physicians were forbidden by Austrian law to perform major operations on patients. The law was sometimes circumvented. The privilege to perform major operations, however, could be purchased in Budapest, Prague, Pressburg and other small towns in Czechoslovakia and Hungary. Consequently, many Americans in Vienna radiated out to these places for opportunities to operate. On one occasion, following a number of casualties, the Budapest City Council passed an ordinance forbidding foreign physicians to operate. The ordinance caused a big fuss for a while, then was all but forgotten, and "out-of-town" medical men were permitted to resume their work in private hospitals. But not without the novitiate surgeon-to-be receiving a mordant thrust from his friends when he left Vienna for a brief stay in Budapest; "So you're off to get your man!"

Most American doctors studying in Vienna were affiliated with a local medical association that cooperated with the University of Vienna in arranging courses and in handling cash transactions between the seekers after knowledge and its dispensers. The physicians who composed the transient Vienna group were a mixture from city and country, some already specialists who wished to improve their skill, others general practitioners. They

(Continued on page A-85)

ter the dance...

sal congestion?

those areas where farm work must take prece-ce over everything else, dances are usually held ring the late fall and winter season. Cider and ughnuts are an important part of an old-fashioned n dance, but there are other addenda. Draughty ms, overheated bodies, and walks in the crisp air "take a breather" or to study the moon with one's rtner—all involve attendant hazards, not the st of which is nasal congestion.

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ote: As with certain other widely used nasal decongestants, over-osage may cause drowsiness or deep sleep in infants and young hildren: KEEP OUT OF HANDS OF CHILDREN OF ALL AGES. Do not use rzine Nasal Spray and TYZINE Nasal Solution, 0.1%, in children nder six years. When using TYZINE Nasal Spray in the plastic ottle, it should be administered only in an upright position.

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came not only from the United States but also from Great Britain, Canada, Australia, India, South Africa and China.

One of the Vienna medical group's chief claims to distinction was its ability to award the *Zeugnis*, the elegant certificate which automatically rewarded the doctor who went to Vienna for postgraduate study. The candidate for a *Zeugnis* was presumed to have studied for at least four months and to have completed a minimum of 300 hours of work, the work to be done in a period of six consecutive months. Actually, there was no way to know whether the prospective candidate fulfilled the required number of hours. Nor did anyone care.

When the proper period of time had elapsed, the *Zeugnis* was handed to the postgraduate, the world thereby receiving notice of his accomplishment. It was an engraved sheepskin, ornate with baroque and rococo scrolls, bearing the signatures of all the professors and instructors with whom its owner had studied. The *Zeugnis* became a fitting ornament to decorate the office walls back home. It was the very sign and symbol of a specialist who had "studied in Europe."

Extracurricular activities in pre-World War II Vienna were not without enticement. Of course, cultural activities in the form of visits to museums, the theater and the opera could be had at the drop of the proper admission price. For those who sought it, however, there was always the company of a soft-eyed *Fräulein* to relieve the monotony of nighttime study. And if their hygienic scruples would permit, they could dally with the ladies of the right-hand side of the Kärntnerstrasse (to which the police limited seductive strolling). But for the less amorous, there were always vacations on the beautiful pine slopes of Semmering or the baroque enchantments of Salzburg. Most doctors passed their idle time in conversation at the then existent Café Edison, the rose-curtained coffeehouse where doctors gathered over a mug of *Wiener Bräu* or coffee *mit Schlag*, touching on such topics as how much better the heating system was at home, the price of a taxi ride, and when the depression would end.

Quotable Notables

If brevity is the soul of wit and variety

(Continued on page A-86)

the mark of it, there is ample evidence of both attributes in many humorous quotations dealing with the medical scene. The quotations have come to us down through the years and from all over the earth as witty remarks, salty sayings and epigrams. Their creators mostly have been writers, orators, philosophers, politicians and men of public affairs, and occasionally medical men capable of laughing at themselves. Here is what the *medicognoscenti* have to say—much truth said in jest, some untruth as well.

To begin with, let us consider the human body. "Even the ugliest human exteriors may contain the most beautiful viscera," declared J. B. S. Haldane, the noted English biologist. To Christopher Morley, whose essays, novels and poetry have beguiled many readers, "A human being is an ingenious assembly of portable plumbing." As for Mark Twain, he claimed that "Anatomists see no beautiful women in all their lives, but only a ghastly sack of bones with Latin names to them, and a network of nerves and muscles and tissues inflamed by disease." Ambrose Bierce, the short-story writer whose disappearance in Mexico has never been solved, once defined the diaphragm as a muscular partition separating disorders of the chest from disorders of the bowel. "The brain," according to poet Robert Frost, "is a wonderful organ; it starts working the moment you get up in the morning, and does not stop until you get into the office." But it was left to Anatole France, whose literary revival is long overdue, to express the earthy opinion that "A woman without breasts is like a bed without pillows."

The human race has been concerned with birth and death for more years than it cares to remember. "How beautifully everything is arranged by nature," asserted Jules Michelet, the nineteenth-century French historian. "As soon as a child enters the world, it finds a mother ready to take care of it." According to "Kin" Hubbard, the newspaper humorist who created "Abe Martin," "About the only thing we have left that actually discriminates in favor of the plain people is the stork." On the other hand, Wilson Mizner, the *bon vivant* and wit, found himself embarrassed when he was born in bed with a lady. As for death, A. Edward Newton, the essayist, found that "Only when a man is safely ensconced under six feet of earth, with several tons of enlauding granite upon his chest, is he in a position to give advice with any certainty, and then he is silent." Ed Howe, the popular writer, once summed it all up when he said, "When a man dies, and his kin are glad of it, they say 'He is better off.'"

The art of medicine concerns all its practitioners. Advised the immortal William Osler: "Look wise, say nothing, and grunt." And as an addendum he offered: "Taking a lady's hand gives her confidence in her physician." For those who are bursting with pride in their ability to heal, Don Herold, artist and writer, offered this observation: "Doctors think a lot of patients are cured who have simply quit in disgust." The other side of the coin showed in the comment of Dorothy Canfield Fisher, grand old lady of American letters, who wrote, "Some people think that doctors and nurses can put scrambled eggs back into the shell."

Therapy, of course, is one of the principal bases of clinical practice. "The desire to take medicine is perhaps the greatest feature which distinguishes man from animals," William Osler once declared. Hence the belief of John Barrymore, famed and sharp-tongued actor, that "America is the country where you buy a lifetime supply of aspirin for a dollar and use it up in two weeks." Years ago, essayist Charles Lamb stated that "The first water cure was the Flood, and it killed more than it cured." More recently, the late Logan Clendening pointed out that "Surgery does the ideal thing—it separates the patient from his disease. It puts the patient back to bed and the disease in a bottle." Is there room for agreement? Yes, according to Remy de Gourmont, famous French novelist. Said he, "Before undergoing a surgical operation arrange your temporal affairs—you may live."

Medical discovery has been the object of much thinking, profound and not so profound. Michel de Montaigne, one of the great essayists of all time, several centuries ago wrote that "Whenever a new discovery is reported to the scientific world, they say first, 'It is probably not true.' Thereafter, when the truth of the new proposition has been demonstrated beyond question, they say, 'Yes, it may be true, but it is not important.' Finally, when sufficient time has elapsed to fully prove its importance, they say, 'Yes, surely it is important, but it is no longer new.'"

Special Issue

Postgraduate Medicine

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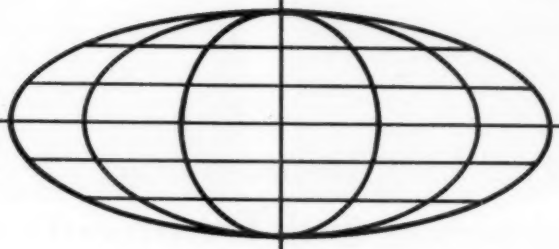

Australia

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The problem of rashes produced by absorption of some drugs is far from solved. The author cites various examples to support the contention that cutaneous changes seem to depend more on biochemical factors than on anything else. The physician may prevent drug reactions in many patients by obtaining an adequate history and offering sensible advice. Suggestions are presented for local treatment and for managing special types of eruptions.

Drug Eruptions; Their Causation and Treatment

G. A. GRANT PETERKIN*

Royal Infirmary, Edinburgh

G. A. GRANT PETERKIN

WHAT are drug eruptions? This term or dermatitis medicamentosa should not include true contact dermatitis, but should be used in referring solely to rashes produced by the absorption of some drug. This absorption may occur in many different ways—not only by injection or oral administration but also by inunction, by inhalation, by enema, through vaginal epithelium, through mother's milk, and so on.

There are few drugs which have not evoked an eruption at one time or another, but some are particularly liable to do so. Our main concern is with these, and they can produce almost any known form of dermatosis. As Sir William Osler said, drugs are double-edged weapons, and dermatologists realize only too well that the first sign of a drug's toxic action may be a rash which may foreshadow grave illness or even death. For nondermatologists in Britain, the paper by Sneddon and Leishman[1] on severe and fatal barbiturate reactions was a timely warning. According to statistics for England and Wales published in 1955, adverse reactions to drugs accounted for 24 of the 149 deaths due to medical or surgical treatment.

What, then, is the mechanism of drug eruptions and how can the various cutaneous manifestations be explained? At present this problem is far from solved, and those who attempt to read about this subject will soon realize that it is wrapped in mystery.

Some patients appear to have a true idiosyncrasy which may be inherited, as exemplified by a woman with a fixed drug eruption due to aspirin who discovered that her father too had reacted to the same drug, in the form of a gastric allergy. In other cases trauma plays a precipitating role, as in a patient in

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FIGURE 1. Pigmented barbiturate reaction on the site of a healed sebaceous cyst.

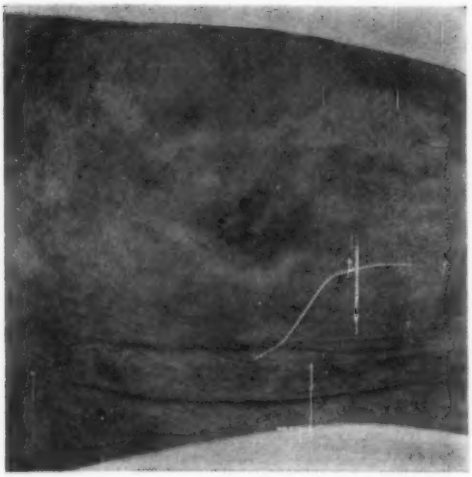

FIGURE 2. Extensive dermatitis due to oral mercurial diuretic, showing desquamation especially in flexures, and pigmentation.

whom a pigmented barbiturate reaction developed on the site of a healed sebaceous cyst (figure 1) or another who had a sulfonamide fixed drug rash on a hand previously affected by a primrose dermatitis. In the same way an ATABRINE® reaction might first appear on a foot with an active fungous infection.

Poor excretory function is liable to be a factor, e.g., in a patient with nephritis or polycystic kidney; and I have been impressed by the many patients with drug eruptions who are extremely constipated. Liver damage, affecting the organ's detoxicating power, sometimes makes the person more liable to cutaneous lesions. For example, a typical heavy metal dermatitis developed in a woman who was taking chlormeredrin, an oral mercurial diuretic, for the treatment of cardiac failure (figure 2).

Exacerbation of a fungous infection following the administration of antibiotics, first described by Feinberg,[2] can be explained as a sensitization reaction to a fungal product, while in other cases fungous infections, especially infections with *Candida albicans*, may flourish because of the disappearance of pyogenic organisms and also because of the interference with the manufacture of vitamin B complex in the gut.

Purpuric reactions to drugs are not uncommon and can be caused not only by the drugs listed in table 1 but also by urea derivatives such as carbromal, bromvaletone and SEDORMID®. Ackroyd,[3,4] in a series of interesting experiments to determine the mechanism of rashes due to these urea products, showed that the drugs had a lytic action on the platelets, rendering them antigenic, and that patch tests in some of the patients provoked a local purpuric reaction. A similiar positive patch test occurred in men who had recovered from purpuric sulfonamide rash.[5]

At one time, the fact that the liver, kidneys and lymph glands were involved in drug eruptions appeared to indicate that interference with the reticuloendothelial system might be responsible. Authorities such as Burnet and Fenner[6] believed that the production of antibody was not a function of a single cell type but a complex activity of more than one form of cell, taking place in situations where phagocytic cells of the reticuloendothelial system are associated with lymphocytes and undifferentiated mesenchymal cells. However, according to Cameron and Spector[7] there is experimental evidence of the production of antibody in the skin, fat, voluntary muscle and cornea, but not in the liver, spleen or bone marrow of

FIGURE 3. Quinine reaction; a contact dermatitis reactivated by ingestion of the drug.

(Acknowledgments are due to *The Edinburgh Medical Journal* for figures 1 and 3, and to Mr. T. C. Dodds, F.R.F.P.S., for all the illustrations.)

rabbits. According to Ehrich and Harris,[8] "the cells which form antibodies have not yet been definitely identified, though some hold that cells of the reticulo-endothelial system are involved . . . on the contrary, there are observations which are not in agreement with this concept." Experiments by Ehrich and Harris indicated that the tissue response accompanying formation of antibodies was chiefly a lymphocytic one, and they pointed to the lymphocytes as a factor in formation of antibodies. Work by Harris and associates[9] indicated that the lymphocytes either produce antibodies or take them up from the lymph plasma, but acquisition of antibody from lymph fluid was not demonstrated, though the reverse was.

Recrudescence of a pre-existing contact dermatitis, such as is occasionally seen after penicillin injections, indicates a genuine allergic response. A parallel case is that of a man who first had a contact dermatitis due to a quinine pessary and whose eruption could be reactivated by taking any quinine preparation by mouth, even an aperitive such as quinquina (figure 3). Haxthausen[10] has shown in a series of tests that the lymphocyte plays a major role in the reaction of a contact dermatitis.

As Huriez[11] said, the progress of biopathology more and more makes it apparent that disease can be regarded as an upset of cellular metabolism, and that we are just beginning to know the successive stages in the disintegration of drugs.

The brilliant work by Peters and his colleagues opened up a new vista, and it would seem likely that these cutaneous changes depend more on biochemical factors than anything else. Peters[12] tested the effect of dichlorodiethyl sulfone, which resembled the effect of iodoacetic acid, in developing the theory that vitamin B_1 is a specific factor in the oxidative system of pyruvic acid. During World War II, Peters, Stocken and Thompson[13] elaborated the theory that a biochemical lesion in a tissue faced by the partial blocking (as by the partial deficiency) of an enzyme system can cause pathologic changes. The poison produced in effect an enzyme deficiency, the attack being on essential –SH groups in this enzyme protein. That interference with the degradation of carbohydrate at the pyruvate stage was serious for tissue cells was supported by the low concentrations of arsenical to the pyruvate and by the accumulation of pyruvate in the blood produced by arsenical poisoning. Peters and his co-workers showed that inhibition of such an enzyme by a vesicant like lewisite was the first step toward formation of a bulla.

Further evidence for the "enzyme theory" was produced by Dixon and Needham,[14] who showed hexokinase to be an –SH enzyme readily inactivated by oxidation and reactivated by cysteine, and sensitive, though only in the reduced form, to lacrimators and the arsenicals. The chemicals they used included methyl bromide. Lerner[15] referred to the recent work on the occurrence of these enzymes in the skin of humans and rats, i.e., hexokinase, triose phosphate, dehydrogenase and enolase, and to the vitamins such as riboflavin and nicotinamide acting as co-factors. Enzymes regulate the rate of each step with such vitamins as thiamine, riboflavin, nicotinamide, pyridoxine and pantothenic acid acting as coenzymes in the oxidative phase of metabolism. In some reactions more than one of these may be involved, which may explain

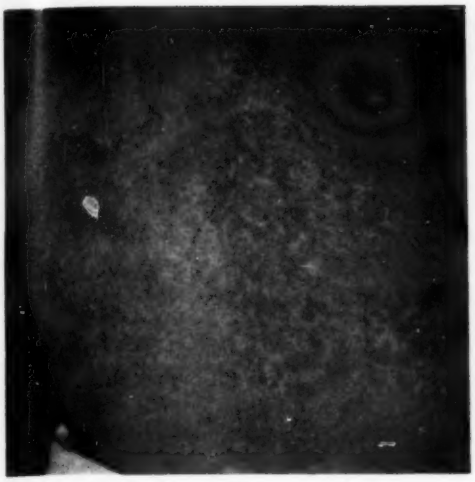

FIGURE 4. Typical chloral rash.

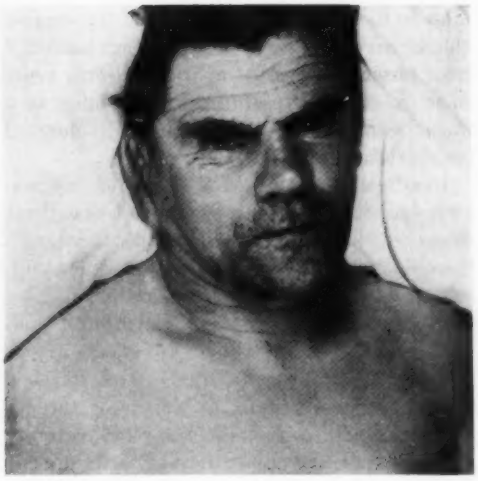

FIGURE 5. Sulfonamide light dermatitis with scarlatiniform eruption on covered areas.

the differences in clinical appearances of rashes. Vesicating agents in general bind sulfhydryl groups and inactivate enzymes, but so far the true reason for the nonadherence of cells and the formation of bullae is not known. Baldwin[16] mentioned that recent work indicates that the complex system of enzymes and co-factors is associated mainly with the mitochondria of cells, as suspensions of washed intact mitochondria can catalyze all the events which compose the cycle, but the particles can be disintegrated to some extent, for example, by treatment with fat solvents which liberate some of the enzymes. In due course it may be proved that interference with the molecular linkage of desoxyribonucleic acid has played a major part.

These changes appear to be nonspecific, for dermatitis medicamentosa rarely gives rise to characteristic lesions, though it is often easy to diagnose the fixed drug eruption caused by phenolphthalein and to suspect that a scarlatiniform one is due to ingestion of either morphia quinine chloral (figure 4) or sulfonamides (figure 5). More often dermatologists have to confess that drug rashes are nonspecific and that similar dermatoses can be produced in the same patient at different times by medicaments not closely related chemically.

Development of bullae due to arsenical vesicants can be paralleled by bullous drug eruptions. For instance, in the severe bullous reactions to barbiturates and the closely related hydantoin compounds a similar biochemical change may occur. As a parallel effect involving other tissue than the skin, Girdwood and Lenman[17] described a megaloblastic anemia in a woman treated for epilepsy with phenobarbital and primidone with good response to folic acid. They concluded that either or both of these drugs might, under some circumstances, act as competitive inhibitors of some enzyme system normally involving folic acid as a co-factor.

When we consider that Peters and his colleagues have demonstrated that arsenic and other heavy metals can be liberated from cells by the administration of dimercaprol (British anti-lewisite), so that they no longer interfere with enzyme action, and that these drugs can produce many different types of rash in the same person, it is logical to assume that what applies to bullous reactions may well apply to other kinds. For example, morbilliform eruptions, which may be observed in association with other types of drug rash, e.g., sulfonamide light dermatitis, also frequently occur by themselves after minimal dosage of a barbitu-

rate. In these cases overactivity of the eccrine glands may act as a precipitating factor; I have observed a series of morbilliform eruptions in women hyperhidrotic after labor in a warm ward after receiving a single dose of butabarbital.

Heathcote[18] discussed the role of sulfonamides in dermatology and stressed that these drugs are closely related chemically to vitamin B complex—sulfapyridine to nicotinic acid, sulfadiazine to riboflavin, while a thiazole ring occurs in thiamine. He noted that Fildes[19] had suggested that some of the toxic effects of sulfonamides might be due to their interference with an enzyme system, by depriving the enzymes of their co-factors. Many sulfonamide reactions have the appearance of a vitamin deficiency, e.g., pellagra or ariboflavinosis, as can happen with other drugs such as antibiotics, barbiturates and even some antihistamines, but one must remember that the neuritis that may develop following administration of isoniazid is due to interference with pyridoxine and not nicotinic acid.

No doubt the pigmented lesions in fixed drug eruptions can be explained in a similar way, and during recent years much light has been shed on the chemistry of cutaneous pigmentation. Burns[20] pointed out that sulfhydryl groups prevent pigmentation and so it occurs in chronic arsenical poisoning. It is supposed that the normal adrenal gland helps maintain a high concentration of sulfhydryl groups in the skin and thus pigmentation is prevented. The efficacy of corticosteroids in severe drug rashes illustrates this point. Not only the skin but also other tissues may pigment through the action of drugs. Examples are the subungual staining due to phenolphthalein described by Campbell,[21] the staining of a tooth due to Atabrine described by Peterkin,[22] and the Atabrine effects described by Wilson[23] and Lutterloh and Shallenberger,[24] whose patients had involvement of the hard palate, nasal cartilage, gums and subungual areas. Lutterloh and Shallenberger[24] commented on the similarity to the pigmentation associated with ochronosis, and Fitzpatrick[25] stated that ochronosis is most probably caused by absence of an enzyme that is normally required for the oxidation of homogentisic acid, formed from tyrosine.

Therapy of Drug Eruptions

Prevention—With care on the part of the doctor, many patients could be spared the affliction of a drug reaction. Before prescribing medicaments, it is the duty of the physician to obtain an adequate history from the patient regarding adverse reaction to chemicals. For instance, a pre-existing sulfonamide dermatitis may be reactivated by flavine, cocaine derivatives, para-aminosalicylic acid, and so on; and a penicillin urticaria was reproduced by the small amount of the drug in poliomyelitis vaccine.[26] Potent drugs should not be prescribed unless there is a definite indication for their use, and if there is a choice of effective remedies the one least likely to cause side effects should be employed. If the risk of a severe reaction to a drug is great and its exhibition extremely desirable, corticosteroids may be invaluable, e.g., in a person gravely ill with tuberculosis and sensitized to streptomycin. Desensitization to specific drugs should be undertaken only under hospital conditions by an experienced physician, as the process is by no means easy and at times is even hazardous. Probably the most successful results are obtained with sulfonamides, penicillin and streptomycin, but only too often the results are not satisfactory, and, in general, it is wiser to inform the patient clearly regarding his sensitivity, giving him a letter to show to any doctor who at some future date may wish to give him similar medication.

General principles—The essential is to use plenty of common sense in handling the case as a whole. Not only the drug apparently responsible for the rash but also all other medicaments must be stopped if possible. A high temperature and lymphadenitis are frequently due to the drug reaction, not to infection, and soon subside with no treatment whatever. If a sedative is required, a nonbarbiturate one should be given, of a type little liable to produce side effects, and even antihistamines should be regarded with suspicion for they also can produce rashes.

Many of these patients are very constipated,

TABLE 1

Compilation From Various Sources of Characteristic Reactions to Certain Drugs

DRUGS	TYPES OF RASH																								
	Urticarial	*Purpuric*	*Morbilliform*	*Scarlatiniform*	*Vesicular*	*Pustular*	*Bullous*	*Seborrheic dermatitis*	*Contact-type dermatitis*	*Eczematoid*	*Exfoliative dermatitis*	*Photosensitivity*	*Dermatophytid*	*Pityriasis rubra pilaris*	*Erythema multiforme*	*Stevens-Johnson syndrome*	*Erythema nodosum*	*Lupus erythematosus*	*Periarteritis nodosa*	*Nodular vasculitis*	*Ulcerative or granulomatous*	*Lichenoid*	*Psoriasiform*	*Fixed drug eruption*	*Mucosal lesions*
Barbiturates	x	xx	xxx	x	x	x	x			x	xx	xx			xx	xx								xx	xx
Hydantoin		x	xxx	x			x				x								xx						x
Penicillin	xxx	x	x	x			x	xx	xx	x	x	x	xx		x	x	x		x	x				x	x
Streptomycin	xxx	x	x	x	x		x	xxx	x	x	xx	xx	x						x	x					xx
Other antibotics	x							xx	x	x		x	x		x				x	x				x	x
Sulfonamides	x	x	xx	x	x	x	x	xx	xx	x	x	xxx			x	x	x	x	x	x			x	x	x
Heavy metals	x	x	x	x	x		x	x		x	xx	x	x	x					x			xx		x	x
Halogens	x	xxx	x	x	xx	xx	xx				x				x		x				xxx			x	x
Salicylates	xxx	xx	xx	x	x		x		x	x									x	xx				x	x
Quinine	x	x		xxx			x	x	x	x	x													x	x
Quinacrine		x	x	x			x	x		x	xx	x	x	xx				x				xxx	x	xx	xx
Phenolphthalein	x	x					x			x					x									xxx	x

so that a brisk purge is indicated, and the diet should be light and easy to digest. Copious intake of bland fluids may aid the excretory functions, and sudden changes of temperature should be avoided. All potentially irritating local applications should be avoided, and any made should be of a nature indicated for whatever dermatosis the eruption most closely resembles; e.g., a weeping eczematous condition should be treated by soothing, slightly astringent wet dressings such as Burow's solution.

Patients with minor reactions can continue their normal mode of life and only need to stop taking the drug, but more severe reactions frequently require hospitalization, as skilled nursing is of the utmost importance. Antihistamines can be expected to relieve symptoms only in cases of rashes with an urticarial element and should not be given routinely. In general, vitamin therapy is disappointing but may be helpful in certain reactions. Cortisone and related substances should not be used haphazardly but only if there is good reason for prescribing them.

Management of special types of eruptions—Many different drugs can cause severe rashes, but the ones most likely to be responsible are (1) the heavy metals such as arsenic, gold, bismuth and antimony; (2) the sulfonamides and chlorpromazine; (3) the barbiturates and anticonvulsants, such as diphenylhydantoin sodium (DILANTIN®), methylphenylethyl hydantoin (MESANTOIN®), and trimethadione (TRIDIONE®); (4) the antibiotics (penicillin, streptomycin, AUREOMYCIN®, tetracycline, etc.); (5) halogens, especially bromides and iodides; (6) antimalarials including Atabrine (mepacrine), quinine, chloroquine and CAMOQUIN®; (7) urea derivatives like Sedormid, bromvaletone and carbromal; (8) phenylbutazone (BUTAZOLIDIN®), still occasionally prescribed in rheumatoid arthritis; (9) antipyrine, usually producing an innocuous fixed drug eruption but sometimes, as in the notable series described by Kennedy and associates,[27] causing a serious extensive bullous dermatosis.

The heavy metals can cause a variety of rashes, such as lichenoid, seborrheic and exfoliative dermatitis. The introduction of dimercaprol (British anti-lewisite) was a valuable therapeutic aid, and the drug is best given at an early stage in a dosage of 2.5 mg. per kilogram at four hour intervals for two successive days, followed by two injections on the third day and one or two injections daily for 10 days or until recovery. However, one should not forget that dimercaprol is itself a toxic substance and that it is of no value in lead poisoning. In some cases treatment with corticosteroids or transfusions with whole blood or plasma may be advisable, but in most cases bland dressings such as zinc paste or calamine liniment applied by skilled nurses are the main requirement.

The steroids may also be indicated for any patient who manifests severe toxic symptoms such as may occur with the administration of any of the aforementioned drugs. The appearance of bullous lesions, exfoliative dermatitis, Stevens-Johnson syndrome, lupus erythematosus or periarteritis nodosa may warrant their use in adequate dosage.

Photosensitivity such as may occur with sulfonamides, chlorpromazine, streptomycin and barbiturates may persist not only for months but even for years after the drug has been discontinued, so it is advisable to treat these patients in a darkened room and to subject their skin to gradually increased exposure to daylight until they can tolerate a full hour in bright sun. Parasol creams are of little value and those containing para-aminobenzoic acid can in fact precipitate relapse of a sulfonamide reaction. Nicotinic acid is notably effective in reactions resembling erythema multiforme with light sensitivity, and most if not all cases of Stevens-Johnson syndrome will respond quickly to a dosage of 50 mg. four times a day. In this disorder the administration of potent drugs such as antibiotics is to be deprecated, as they are likely to do more harm than good.

Vitamin B complex has been advocated in many kinds of drug rash and has the great advantage that if it does no good it can do no harm. Patients with lesions suggestive of vitamin B deficiency such as cheilitis, angular stomatitis and glossitis may benefit, and it is always desirable to prescribe large doses for persons treated with oral antibiotics. In these patients, infections of the skin due to *C. albi-*

cans may occur, when not only vitamin B should be prescribed but also nystatin tablets, four daily, and nystatin ointment locally. Vitamin A, 50,000 units twice or thrice daily, can be useful for dermatoses showing follicular or other hyperkeratosis, dryness or lichenoid lesions. In purpuric eruptions such as those due to the halogens or urea compounds, large doses of vitamin C can be given as ascorbic acid and rose hip syrup, sometimes with apparent benefit. If thrombopenic purpura is diagnosed, blood transfusions and hematinics such as vitamin B_{12} and folic acid may be required.

Antihistamines have no curative value and should therefore be used only as symptomatic treatment for rashes with some urticarial element. Acute giant urticaria, which can be activated by many drugs but most commonly is due to penicillin and aspirin, frequently responds better to a few injections of ADRENALIN® (1:1000) or to ephedrine hydrochloride, ½ gr. thrice daily.

Local treatment—The type of rash determines the form of local applications, which should be similar to those used for the disease imitated by the drug eruption. For exudative vesicular or bullous conditions one can recommend compresses of Burow's solution, diluted 1:10 with sterile water, or 0.5 per cent silver nitrate; 0.5 per cent hydrocortisone skin lotion; and paints such as 0.5 per cent eosin solution, with a spread dressing of petrolatum containing 12 per cent zinc oxide on top. For erythematous and papular eruptions, shake lotions dabbed on several times daily are all that is needed, e.g., 2 per cent ichthammol in calamine lotion or the hydrocortisone lotion. For infective lesions, such as may occur in the flexures, hydrocortisone or prednisolone can be combined with quinoline drugs (QUINOLOR®, VIOFORM®, STEROSAN®); antibiotics (soframycin, neomycin); or quaternary ammonium compounds (e.g., domiphen bromide 0.05 per cent). For exfoliative dermatitis, applications of a dye such as 0.5 per cent eosin or gentian violet covered with complete spread dressings of zinc paste usually do well. In acneiform eruptions, 3 per cent sulfur in calamine lotion may be effective.

As a rule, tar preparations are not tolerated well by patients with drug rashes, especially if any element of photosensitization is present, and in general the mildest and most soothing treatments should be preferred, rather than those liable to provoke an adverse reaction.

Summary

It is suggested that blocking of enzyme systems may play an important part in the production of many, if not all, drug eruptions, whether bullous, eczematoid, seborrheic, erythematous, morbilliform or pigmented.

Prevention of a drug rash is often possible, and doctors can do much to protect their patients from such reactions by taking careful histories and giving sensible advice.

Therapy of drug eruptions is discussed under the headings of prevention, general principles, management of special types, and local treatment.

REFERENCES

1. SNEDDON, I. B. and LEISHMAN, A. W. D.: Severe and fatal phenobarbitone eruptions. Brit. M. J. 1: 1276, 1952.
2. FEINBERG, S. M.: Penicillin allergy; on probability of allergic reactions in fungus-sensitive individuals; preliminary experiments. J. Allergy 15:271, 1944.
3. ACKROYD, J. F.: Pathogenesis of thrombocytopenic purpura due to hypersensitivity to Sedormid (allyl-isopropyl-acetyl-carbamide). Clin. Sc. 7:249 (April) 1949.
4. ——: Purpura due to hypersensitivity to Sedormid (allyl-isopropyl-acetyl-carbamide). Proc. Roy. Soc. Med. 46:261, 1953.
5. PETERKIN, G. A. G.: Sulphonamide rashes; analysis of 500 cases seen in North Africa and Italy. Brit. M. J. 2:1, 1945.
6. BURNET, F. M. and FENNER, F.: The Production of Antibodies. Ed. 2. New York, The Macmillan Company, 1949, p. 62.
7. CAMERON, G. R. and SPECTOR, W. G.: In MACKENNA, R. M. B. (ED.): Modern Trends in Dermatology. Second series. London, Butterworth & Co., Ltd., 1954, p. 72.
8. EHRICH, W. E. and HARRIS, T. N.: Formation of antibodies in popliteal lymph node in rabbits. J. Exper. Med. 76:335, 1942.
9. HARRIS, T. N., GRIMM, E., MERTENS, E. and EHRICH, W. E.: Role of lymphocyte in antibody formation. J. Exper. Med. 81:73, 1945.
10. HAXTHAUSEN, H.: Allergic eczema. In LOEWENTHAL, L. J. A. (ED.): The Eczemas. Edinburgh, E. & S. Livingstone, 1954, p. 42.
11. HURIEZ, C.: Les facteurs des accidents generaux d'intolerance aux medications chimiques et antibiotiques. Semaine hôp. Paris 31:1, 1955.

12. Peters, R. A.: Biochemical lesion in vitamin B_1 deficiency; application of modern biochemical analysis in its diagnosis. Lancet 1:1161, 1936.
13. Peters, R. A., Stocken, L. A. and Thompson, R. H. S.: British anti-lewisite (BAL). Nature, London 156:616, 1945.
14. Dixon, M. and Needham, D. M.: Biochemical research on chemical warfare agents. Nature, London 158:432, 1946.
15. Lerner, A. B.: Enzymes. In Rothman, S.: Physiology and Biochemistry of the Skin. Chicago, University of Chicago Press, 1954, p. 566.
16. Baldwin, E.: Dynamic Aspects of Biochemistry. Ed. 2. London, Cambridge University Press, 1952, p. 449.
17. Girdwood, R. H. and Lenman, J. A. R.: Megaloblastic anaemia occurring during primidone therapy. Brit. M. J. 1:146, 1956.
18. Heathcote, R. S. A.: Role of sulphonamides in dermatology. Brit. J. Dermat. 56:59, 1944.
19. Fildes, P.: Rational approach to research in chemotherapy. Lancet 1:955, 1940.
20. Burns, J. H.: Pigmentation of skin. Brit. J. Dermat. 63:431, 1951.
21. Campbell, G. G.: Peculiar pigmentation following use of purgative containing phenolphthalein. Brit. J. Dermat. 43:186, 1931.
22. Peterkin, G. A. G.: Mepacrine drug eruption affecting tooth. Brit. J. Dermat. 61:287, 1949.
23. Wilson, D. J.: Eczematous and pigmentary lichenoid dermatitis; atypical lichen planus; preliminary report. A.M.A. Arch. Dermat. 54:377, 1946.
24. Lutterloh, C. H. and Shallenberger, P. L.: Unusual pigmentation developing after prolonged suppressive therapy with quinacrine hydrochloride. A.M.A. Arch. Dermat. 53:349, 1946.
25. Fitzpatrick, T. B.: Ochronosis. A.M.A. Arch. Dermat. 63:796, 1951.
26. "Any Questions?" Brit. M. J. 2:55, 1957.
27. Kennedy, C. B., Davis, F. H., Hennington, V. M. and Sternberg, M. J.: Dermatitis medicamentosa due to antipyrine. A.M.A. Arch. Dermat. 75:826, 1957.

Postgraduate Clinical NOTES

104. ITCHING

One of the most urgent symptoms in dermatology is itching, and the preparations which claim to relieve this symptom give us many disappointments. The antipruritics of the -caine group are some of the most noxious. Cinchocaine, Amethocaine, Benzocaine and a number of similar substances have no place as local applications in eczema; they are potent sensitisers, and they distract attention from the fundamentals of treatment, if by any chance they should appear to give temporary relief.

In the same category come the antihistamine ointments, which have no curative effect on the eczemas, and whose antipruritic action should be reserved for insect bites. They are only weak antipruritics but they are powerful sensitisers.

If a patient's itch is severe enough to demand these local antipruritics, then what he really needs is rest and sedation; if he gets unduly clamorous, then it is possible that he is mentally ill and that he needs expert psychiatric as well as physical treatment. The really bad case of eczema, with gross oedema, generalised weeping and severe exfoliation, is fortunately becoming rarer now that syphilis is being treated without arsenic, and gold is being recognised by the rheumatologists as one of the baser metals; but such patients can usually be relieved dramatically by the use of systemic cortisone or corticotropin. I mention this parenthetically, lest anyone should think that I am advocating a policy of masterly inactivity, even in these severe cases; their active treatment is anything but disappointing.

R. E. Bowers, Disappointments in dermatology, *The Lancet*, January 4, 1958, pp. 43-45

Studies at the Dunedin clinic indicate that preventive treatment of hypertension should start when the basal blood pressure is high. Treatment must be highly individualized and include long-term studies of the patient's responses. Side effects of powerful drugs complicate adequate control of blood pressure. Ganglion-blocking agents combined with reserpine or other Rauwolfia alkaloids have been effective. Evidence suggests a decrease in the incidence of strokes in patients maintained on full treatment.

Basic Principles of Hypotensive Therapy

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THE immense literature on the subject of hypertension and its recent great increase must surely reflect the intellectual satisfaction to be derived from working in a field that is advancing and is ripe for further advancement. The human rewards from treating patients with this group of disorders are also considerable, for now we possess the means of relieving many of the manifestations of hypertension and of preventing or retarding the development of some of its complications.

The pathogenesis of essential hypertension is imperfectly understood, yet much is known. Hypertension is not only a symptom but is an intermediate cause. Whatever factors are responsible for raising the blood pressure, it is apparent that the hypertension, once it is of sufficient degree and persistence, causes or predisposes strongly to the development, secondarily, of such manifestations as headaches, encephalopathic attacks of various kinds, dizzy attacks, strokes, retinal changes, circulatory changes giving rise to cardiac asthma, congestive heart-failure, breathlessness on exertion, an enhanced tendency to angina, frequent nosebleeds and in some instances alterations in renal function.

It is to be expected that ultimately we shall have more complete understanding of the relation between the causation of the various forms of hypertension and their treatments. Meanwhile we may quote Samuel Butler: "Life is the art of drawing sufficient conclusions from insufficient premises."

In this article, I will not attempt to discuss the details of treatment but rather I shall say something about whatever principles (or precepts) seem to be available for our present guidance.

Alternatives Available to the Patient and Doctor

In broad outline the alternatives available include (1) a general assurance to the patient

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that all is well, (2) a hope that simple measures, e.g., reserpine alone, will suffice, and (3) a firm decision that effective reduction of blood pressure is in the patient's long-term interest and should be embarked on in full knowledge of the problems and hazards.

A considered choice among the alternatives depends on an estimate of the prognosis, always a hazardous computation. There are those who would have us assure the majority of our patients that a high blood pressure is a physiologic variant and who consider that the best we can do is recommend that they forget about it if by chance some other physician has alerted them to the disadvantages of hypertension. On the other hand there are those who consider that an elevated blood pressure renders the expectation of health and life a short one. Reviewing such writings, it seems that the divergent views about prognosis may be related to the types of patients the authors have seen. Random surveys of blood pressure levels reveal that many patients with high casual blood pressures have a long life expectancy. Usually, however, patients referred to clinics because of definite hypertensive symptoms, even though their blood pressures are no higher than those in mild cases, have, when untreated, a poor outlook.

The high probability that the outlook for patients with fixed hypertension is less satisfactory than it is for patients with labile hypertension has long been part of medical thinking. A standardized method of measuring the basal blood pressure[1] has provided an index of the degree of lability. For about 12 years in our Dunedin clinic almost all patients investigated for hypertension have had a basal blood pressure determination performed by a standardized technic as a routine part of the study, and the subsequent progress of approximately 270 patients has been examined after 8 to 12 years. It has become apparent that the outlook as regards survival is more closely related to the basal blood pressure than to the casual blood pressure. The basal blood pressure has the advantage that on repetition in normal subjects and persons with mild hypertension there is little variation from one occasion to another.[2] Indeed the basal blood pressure is almost a physiologic constant for the individual.

The difference between the casual blood pressure and the basal blood pressure we have described as the supplemental blood pressure. A study of our untreated follow-up series indicates that whereas there is a close relationship between the basal blood pressure and the outlook as regards life, there is little correlation at five years (indeed, a slightly negative correlation) between the height of the supplemental pressure and the outlook. Thus the casual blood pressure is the sum of the basal blood pressure, which influences prognosis, and the supplemental blood pressure, which has but little or no influence on a five year prognosis.[3]

There is also a close correlation between the height of the basal blood pressure and the occurrence of such important manifestations as breathlessness, heart-failure and the presence of electrocardiographic and retinal abnormalities. This observation is consistent with a view expressed by many physicians, that the outlook in hypertension may be more closely related to the existence of secondary manifestations than to the level of the casual blood pressure. Even so, to wait for the appearance of significant breathlessness, advanced retinal changes or heart-failure, or indeed the occurrence of a stroke before starting treatment is hazardous to the patient. The relation of the level of the basal blood pressure to life expectancy demonstrated in our series has convinced our group of the desirability of undertaking treatment in patients whose basal blood pressure is high, even if significant symptoms are lacking.

One cannot easily lay down rules about the stage at which preventive treatment should be undertaken. The decision usually should be the subject of discussions between patient and physician. I am confident that determination of the basal blood pressure under standardized conditions is of the utmost importance in making the decision.

It is likely that better methods of treatment will be developed, involving fewer side effects and less need for meticulous control of the regimen by patient and doctor. When they

are, it is to be expected that treatment directed to the prevention of secondary manifestations will be undertaken at an earlier stage.

Extent to Which Hypotensive Therapy Can Relieve Hypertensive Manifestations

The willingness of doctors and patients to undertake a complicated regimen of treatment requiring regular supervision and associated in some instances with significant side effects must be related to the expectation of improvement in symptoms or outlook. Symptomatic improvement may be obtained by degrees of reduction of blood pressure which probably do not influence the long-term prognosis appreciably, but as modest falls of blood pressure can be obtained with smaller doses of powerful drugs the side effects are correspondingly less conspicuous.

With few exceptions the practice of our clinic has been first to maintain the blood pressure as near as practicable to an ideal normal, and second to adopt measures designed to lessen or eliminate side effects. Most of the time of the clinic is spent adjusting the regimens with the object of improving the comfort of patients while preserving adequate control over blood pressure levels.

In this, no simple routine enables the physician to have success. The means used must be highly individualized and the physician using them must be grounded in the relevant fundamentals of pharmacology and physiology. Maintenance of treatment depends on the combined efforts of patient and doctor; their close collaboration is essential. In most instances after several months or a year the treatment becomes easier and more comfortable to the patient. We have found, as have Perry and Schroeder,[4] that in many cases the requisite doses of drugs diminish, but occasionally there has been an increase.

I cannot emphasize too strongly that the results to be obtained from hypotensive therapy, especially when ganglion-blocking drugs are used, depend on maintenance of a close control over blood pressure levels. Close control over the blood pressure with comparatively few side effects will seldom be obtained without the exercise of a technic that is rather more exacting but even more rewarding than that of a well-run diabetic clinic.

It is generally recognized that effective hypotensive therapy should lead, with few exceptions, to dispersal of hemorrhages and exudative changes from the retina and to relief of cardiac asthma in virtually all cases and of general congestive heart-failure in most cases, without resort to other measures such as digitalis and strong diuretics.[5]

There is evidence that some hypertensive manifestations are prevented or postponed. Those who have treated large numbers of patients with severe hypertension who presented without congestive heart-failure have been struck with the low incidence subsequently of heart-failure and cardiac asthma among adequately treated patients.[6,7] Deaths in our series are usually from coronary disease, uremia and stroke. In the years 1950 to 1953, when control over the blood pressure was less satisfactory than it is now, the incidence of deaths from heart-failure in our series was very low but that of deaths from strokes was high. With better control over blood pressure levels in recent years the incidence of strokes has diminished, but it still accounts for an important proportion of the deaths.[3,8] It is very doubtful whether deaths from coronary disease and renal excretory insufficiency are postponed to a significant degree. Exercise tolerance is improved in over 50 per cent of anginal patients.[9] There seems to be an optimal range for the blood pressure above which symptomatic relief is inconspicuous and below which spontaneous anginal discomforts (relieved by lying flat) occur.

Relief of headaches and vertigo should be obtained in a great majority of patients. Psychologic factors influence the relief of these and other symptoms but drug action seems to play a more important role.

Simple Measures in Mild Cases

In many patients with overaverage pressures, investigation will lead to the conclusion that there is no likelihood of early deterioration and the use of ganglion-blocking drugs would be premature. My practice is to

tell such patients that the blood pressure is overaverage and not a source of danger but as a precaution they should be seen at 6 or 12 month intervals because, were the blood pressure to rise to undesirable levels, treatment could be started before damage to health occurred. In the meantime they should lead full lives consistent with their years, reducing the body weight if overweight and avoiding only activities that would be excessive for a normal person. In some instances 0.25 to 0.5 mg. of reserpine daily is given and this medicament is continued provided it induces a fall of blood pressure in excess of that induced by a placebo. Usually these doses do not lead to mental depression but we mention the possibility and ask the patients to report any side effects. Psychologic problems and environmental strains are discussed usually at a superficial level; more than this is seldom needed.

Treatment by Effective Reduction of Blood Pressure

Unfortunately, at present a good control over the level of the blood pressure means that the doses of the drugs to be administered, usually ganglion-blocking agents, must involve the production of significant side effects in many patients. Fortunately, close control over the regimen and the use of measures designed to lessen or prevent side effects are usually successful in the restoration of comfort. Certainly in substantial cases the subjective improvement due to relief of hypertensive manifestations compensates for any residual discomfort from drugs.

Hypotensive episodes including postural hypotension are not side effects but are manifestations of the desired action of the drug, carried to excess. Hypotension, usually in the morning, is compatible with excessively high pressures at other times. When this occurs there should be an alteration in the distribution of doses, for example, a decrease in the dose taken at breakfast time and an increase in the one at, say, 2 P.M. It is sometimes necessary to accept a mild degree of hypotension at some times in the day in order to be reasonably assured that the blood pressure has fallen adequately at other times. In patients with grade 3 or grade 4 retinopathy the close control over blood pressure levels is of paramount importance, for the heaviest mortality is to be found in these groups even when all exudative retinal changes have disappeared in the course of treatment.

Parasympathetic side effects such as blurring of vision, dryness of the mouth and constipation can be counteracted by such measures as the prescription of positive lenses to be used when there is blurring, and eserine eye drops 1/32 per cent. Pilocarpine by mouth, 1/32 or 1/16 gr. a half-hour before meals, relieves dryness. Laxatives may, when necessary, be assisted with 15 mg. tablets of neostigmine, of which one, sometimes one and a half, may be taken half an hour before breakfast combined with a laxative, administration being timed to produce a peak effect shortly after breakfast.

Reserpine

Reserpine by itself seldom produces an adequate fall of blood pressure in patients whose basal blood pressures are high and who are in real need of treatment. Occasionally this drug induces good falls of blood pressure with safe doses (0.5 mg. daily or less), but its greatest use in treatment of severe hypertension is to enhance the action of ganglion-blocking drugs, thereby making a smaller dose effective with consequent decrease in side effects. Further, the great variability in the blood pressure after ganglion-blocking drugs is reduced to some extent when they are used in combination with reserpine.

At the outset we used routinely 0.5 mg. thrice daily of reserpine in combination with whatever doses of ganglion-blocking drugs proved necessary. The improvement in the degree of control over the blood pressure by this combination was considerable, and even the casual blood pressures at the follow-up outpatient clinic were much improved. Unfortunately it was found[10,11] that with these large doses of reserpine the complication of severe mental depression occurred in as many as 20 per cent of cases, even making its appearance after a year or more of satisfactory

administration. When the dose of reserpine was restricted, 0.25 mg. to 0.5 mg. daily, depression became much less frequent and severe depression uncommon.

Use of certain other *Rauwolfia* alkaloids as an alternative to reserpine proved to be an advantage to certain patients. For example, in some cases such side effects as mild depressions, nightmares or excessive drowsiness have been relieved on transfer to equally hypotensive doses of canescine or rescinnamine.[12] The increase of appetite that often follows the administration of reserpine has been lacking and even replaced by decrease of appetite on transfer to rescinnamine. The dose of canescine used was 1.0 mg. daily or less, and of rescinnamine 0.75 mg. daily or less.

Unfortunately the degree of control over the blood pressure is not as good when 0.5 mg. of reserpine is used as it is with 1.5 mg. I have had the impression that the mortality rate has risen a little since we have had to relax somewhat the degree of control over the blood pressure level. Hence, we are concerned to investigate the possibility of other additions or alternatives that will enable a better and more stable control over the blood pressure. In our clinic this has been attempted by the administration of hydralazine but without much success.

Ganglion-blocking Drugs

As already mentioned, the technic of controlling blood pressure levels by use of ganglion-blocking drugs amounts to an individual bio-assay of the patient's responses to one or more ganglion-blocking agents.

We usually find in starting treatment with these drugs that it is desirable to have patients make all-day attendances at our clinic five days weekly for three weeks. Blood pressures are measured by technicians at half-hour intervals throughout the day in the sitting and standing postures, and the relation between any side effects or discomforts and the blood pressure level is noted. The patients are provided with printed instructions and can discuss their difficulties. After about three weeks they make brief visits weekly, then monthly and then, in well-controlled cases, every three months to insure maintenance of control over blood pressure levels and to enable us to assist in overcoming side effects. For some patients a good regimen can be devised with less expenditure of time, but it is desired to emphasize that the possible benefits from ganglion-blocking drugs cannot be determined without deliberate long-term study of the responses of the individual patient. *Many of the disadvantages ascribed to ganglion-blocking drugs are attributable to an imperfect technic of administration.* We usually find it desirable to change the dosage of drugs by small increments, adjust the times of administration in relation to meals, and allow for alterations in response resulting from drug tolerance and altered physical state.

Consideration will be given to the probability that the patient will be more comfortable and the blood pressure more effectively controlled when the ganglion-blocking drug is combined with a *Rauwolfia* alkaloid.

Development of new ganglion drugs has been of value in that individual patients vary somewhat in their responses; a side effect may be avoided sometimes by changing the drug without loss of control over the blood pressure. In our clinic hexamethonium has been superseded, as we found it usually needed to be given by injection.[13,14] The other well-known drugs are pentolinium (ANSOLYSEN®), chlorisondamine (ECOLID®) and mecamylamine (INVERSINE®). Several drugs that are less well known or still in the experimental stage are of interest and of value to certain patients, e.g., WY-1263 and WY-1395 (Wyeth), IN-395 (Irwin, Neisler) and 139C55 (Presidal).

In general, pentolinium has the advantage of a long trial without the occurrence of significant long-term toxicity. Chlorisondamine resembles pentolinium. Certain patients tolerate alimentary administration better with chlorisondamine than with pentolinium but some feel vaguely less well on the chlorisondamine. Mecamylamine has the big advantage theoretically that it is absorbed almost quantitatively from the alimentary canal and the practical advantage that in some patients control over the blood pressure is smoother and more prolonged. Some patients tolerate oral

mecamylamine though previously other ganglion-blocking agents tried had to be given by injection. In general, however, parasympathetic side effects are rather prominent with mecamylamine, and, exceptionally, patients have had remarkable flapping tremors and severe mental disturbances. We have had one death from this cause.

Some of the differences between individual ganglion-blocking drugs represent responses peculiar to individual patients. For example, a woman patient had severe diarrhea when pentolinium and mecamylamine were given but has been comfortable on WY-1263 and WY-1395. Several patients have had urinary retention while taking mecamylamine but not while taking pentolinium. WY-1395 usually causes more visual blurring than pentolinium but has a somewhat longer action and produces less drug tolerance. Such remarks apply to doses which are equipotent in their effects on the blood pressure.

The details of the methods used to build up a therapeutic regimen for an individual patient are beyond the scope of this paper. A report of the various procedures has been published recently.[3]

It is perhaps worthwhile to refer to eight questions whose answers we think should be affirmative. They provide a rough survey of the adequacy of a patient's regimen when ganglion-blocking drugs are used.

1. Is full use made of posture during both the day and the night? (The patient sleeps in the sitting posture, 45 degrees tilt.)

2. Are blood pressure determinations made in the standing posture?

3. Is there evidence, direct or indirect, that the falls in blood pressure over a 24 hour period are adequate but not excessive; for example, is there avoidance of hypotension at one time and substantial hypertension at others? Casual blood pressure determinations at offices or clinic may be most deceptive.

4. Is there regular supervision of the regimen (say, monthly)?

5. Have all potentially reversible hypertensive manifestations been relieved?

6. Have mimeographed or printed instructions been issued to the patient?

7. Are side effects inconspicuous or at least tolerable?

8. Making allowance for age and irreversible damage (e.g., stroke) before treatment started, has the patient been made happier and more effective?

Summary

A brief account of the basic principles of hypotensive therapy is presented, but without detail.

At present, adequate control over the blood pressure level involves complexity if the side effects of powerful drugs are to be minimized. Most patients can be made comfortable, and there is evidence of life extension in severe cases, relief of potentially reversible hypertensive manifestations, and prevention or considerable retardation of the development of cardiac asthma and congestive heart-failure. There is some evidence suggesting a diminution in the incidence of strokes among patients with very high blood pressures who are maintained on full treatment.

ACKNOWLEDGMENT

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REFERENCES

1. Smirk, F. H.: Casual and basal blood pressures. IV. Their relationship to the supplemental pressure with a note on statistical implications. Brit. Heart J. 6: 176-182 (October) 1944.
2. Kilpatrick, J. A.: The variation of casual, basal, and supplemental blood pressures in health and in essential hypertension. Brit. Heart J. 10:48-56 (January) 1948.
3. Smirk, F. H.: High Arterial Pressure. Oxford, England, Blackwell; Springfield, Illinois, Charles C Thomas, 1957.
4. Perry, H. M. and Schroeder, H. A.: Studies on the control of hypertension. IV. Some evidence for reversal of the process during hexamethonium and hydralazine therapy. Circulation 13:528-536 (April) 1956.
5. Smirk, F. H. and Alstad, K. S.: Treatment of arterial hypertension by penta- and hexa- methonium salts. Brit. M. J. 1:1217-1228 (June) 1951.
6. Shirley Smith, K. and Fowler, P. B. S.: Prevention and treatment of hypertensive heart-failure by ganglion blocking agents. Lancet 1:417-418 (February) 1955.

7. Smirk, F. H., Hamilton, M., McQueen, E. G. and Doyle, A. E.: The treatment of hypertensive heart failure and of hypertensive cardiac overload by blood pressure reduction. Am. J. Cardiol. 1:143-153 (February) 1958.
8. Smirk, F. H.: The treatment of high blood pressure. George Alexander Gibson lecture, delivered in Hall of Royal College of Physicians, Edinburgh, May 1956.
9. Doyle, A. E. and Kilpatrick, J. A.: Methonium compounds in the angina of hypertension. Lancet 1:905-908 (May) 1954.
10. Freis, E. D.: Mental depression in hypertensive patients treated for long periods with large doses of reserpine. New England J. Med. 251:1006-1008 (December) 1954.
11. Doyle, A. E. and Smirk, F. H.: Hypotensive action of reserpine. Lancet 1:1096-1097 (May) 1954.
12. Smirk, F. H. and McQueen, E. G.: Comparison of rescinnamine and reserpine as hypotensive agents. Lancet 2:115-116 (July) 1955.
13. Restall, P. A. and Smirk, F. H.: The treatment of high blood pressure with hexamethonium iodide. New Zealand M. J. 49:206-209 (June) 1950.
14. Kilpatrick, J. A. and Smirk, F. H.: Comparison of oral and subcutaneous administration of methonium salts in the treatment of high blood-pressure. Lancet 1:8-14 (January) 1952.

Postgraduate Clinical NOTES

105. DEATH AFTER SEVERE HEAD INJURY

Of those who survive the accident itself, the main cause of death in patients unconscious after head injury is respiratory insufficiency and anoxia. The anoxia is due to central disturbances of the control of respiration, and reduction of compliance of the lungs by blockage or irritation of the bronchial tree by aspirated material and by retention of mucus.

A regime must be used similar to that laid down for bulbar poliomyelitis:

Correct posture to prevent seepage into the lungs and tracheobronchial tubes.

Temporary intubation.

Isolation of lungs from disorganized pharynx by early tracheotomy.

Their further protection by continued aseptic tracheobronchial toilet.

The use of a lytic cocktail to coordinate the reticular mechanisms of the brain stem, and control rigidity, restlessness and hyperthermia.

Avoidance of oral feeding during unconsciousness.

Maintenance of physiological tensions of oxygen and carbon dioxide in the blood.

Maintenance of fluid and electrolyte balance and calorie intake.

Combating infection by use of antibiotics.

Relief or prevention of secondary cerebral oedema by use of intravenous triple plasma.

It is not enough to wait until the patient reaches a special centre. The important factor is treatment along these lines as soon as possible after the accident.

Ian N. MacIver, Ivor J. C. Frew and J. G. Matheson, The role of respiratory insufficiency in the mortality of severe head injuries, *The Lancet*, February 22, 1958, pp. 390-393

In 70 patients with traumatic ocular nerve palsy, visual axes were restored to parallelism in the primary position by operation on extrinsic eye muscles. Surgical treatment often was carried out in several stages. In unilateral cerebral nerve injuries, the prognosis of normal function was best in fourth nerve palsies, very good in sixth nerve palsies, and only fair in third nerve palsies. Bilateral injuries were more difficult to treat.

The Surgical Treatment of Ocular Palsy Due to Head Injury

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In many cases of ocular palsy due to head injury, spontaneous recovery occurs, but in others there remains a constant deviation of the visual axes associated with diplopia. This article is based on experience of treating 70 patients with ocular palsy due to head injury during the eight year period from 1949 to 1957. In no instance did spontaneous recovery occur, and in every case operation on the extrinsic ocular muscles was carried out, resulting in considerable improvement of symptoms. Binocular single vision was restored in many cases over the whole of the binocular field and in others over a limited area. The prognosis mainly depended on the number of extrinsic ocular muscles affected.

In 48 of the 70 cases there were injuries of cerebral nerves, and in 22 cases an orbital injury caused alteration in the position of the eyeball and a relative defect of movement (table 1). The causes of injury are given in table 2. In the motor car accidents, most of the injuries resulted from the sudden application of the brakes or a collision with another vehicle or lamp post, the patient's head hitting the windshield. Many of these accidents might have been prevented if seat belts had been worn. In the bicycle accidents, usually the patient was riding a bicycle and was knocked down by a motorcyclist or a motorist. The motor bicycle accidents resulted from either skidding or colliding with a motor car.

Symptoms

All but one of the patients had diplopia. In 63 cases it was constant, and in six it occurred only in certain directions of the gaze. The one patient who did not complain of diplopia was a 49 year old woman whose head was injured four and one-half years previously when she fell off a horse. There was complete left sixth cerebral nerve palsy with a resulting left convergent strabismus of 50 degrees. She had not experienced double vision, but merely complained of the unsightly deviation of her left

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TABLE 1

HEAD INJURIES RESULTING IN OCULAR PALSY

Cerebral nerve injury (48 cases)	
Unilateral:	
Third (right 1, left 2)	3
Fourth (right 8, left 15)	23
Sixth (right 6, left 7)	13
Third and fourth, right	1
Third, fourth and sixth, right	1
Bilateral:	
Fourth	2
Sixth	5
	48
Orbital injury (22 cases)	
Defective elevation (right 5, left 10)	15
Defective depression (right 2, left 1)	3
Defective elevation and abduction, left	1
Defective depression and abduction, left	1
Defective depression and adduction, right	1
Defective adduction, left	1
	22

TABLE 2

CAUSES OF INJURY IN 70 CASES OF OCULAR PALSY

Cerebral nerve injury (48 cases)	
Road accidents:	
Motor car accident	25
Bicycle accident	6
Motor bicycle accident	4
Pedestrian knocked down by motor bicycle	2
Miscellaneous accidents:	
Fall from horse	6
Boxing injury	1
Football injury	1
Railway accident	1
Fall down stairs	1
Involvement in public-house brawl	1
	48
Orbital injury (22 cases)	
Road accidents:	
Motor car accident	9
Motorcycle accident	3
Pedestrian knocked down by motor car	1
Miscellaneous accidents:	
Football injury	2
Cricket injury	1
Fall from a roof	2
Operation on nasal sinuses	2
Eye hit by stone	1
Fall on a bucket	1
	22

eye. Although she had normal vision in each eye, she had gross suppression of vision in her left eye. Operation consisting of left medial rectus recession and left lateral rectus resection combined with a muscle transplant of the Hummelsheim type rendered her visual axes approximately parallel, but she continued to suppress the vision of her left eye. The absence of diplopia in this case was thought to be due partly to an unusually dull mentality and partly to the effects of severe concussion of the brain.

In all cases of constant diplopia the patients had worn occluders prior to operation to overcome the disturbing effect of the double vision.

Interval Between Injury and Operation

The interval between the injury and the surgical treatment varied from four months to 35 years (figure 1). The generally accepted rule to wait six months after injury to allow a reasonable period for spontaneous recovery was usually adopted, except where it seemed quite clear from repeated examination of the angle of deviation that the condition was either stationary or getting worse; a gradual increase of the angle of deviation is usually caused by contracture of antagonistic muscles. In many

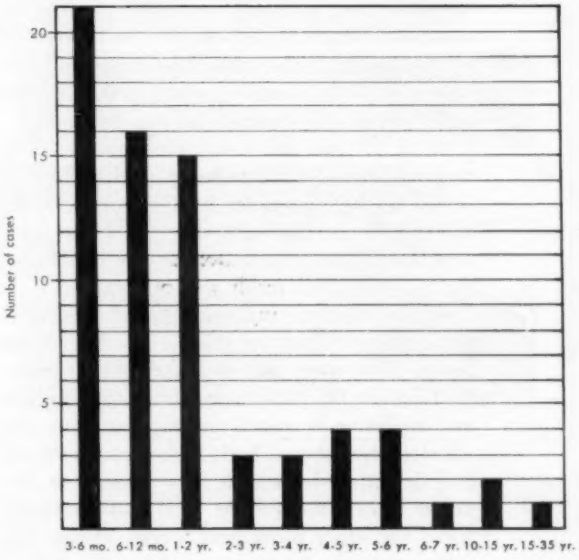


FIGURE 1. Graph depicting the time interval between injury and operative treatment in 70 cases of ocular palsy due to head injury.

cases the interval was much longer than six months, either because the patient did not seek advice or because the operation was postponed for other reasons, sometimes because other injuries had to be dealt with first.

Operative Procedures and Results

It was often necessary to carry out surgical treatment in more than one stage. Sometimes three or four operations were required before a satisfactory result was obtained. The possibility of several operative stages should always be explained to the patient before treatment is begun.

The aim of surgical treatment in ocular palsy is to restore as nearly as possible a state in which the movements of the two eyes are symmetrical and equal. It is rarely possible to restore full function to a partially paralyzed muscle, but it is quite possible to improve that function by weakening the action of its direct antagonist and sometimes by directly strengthening its action. It is also possible to weaken the overaction of the contralateral synergist so that the corresponding movement of the unaffected eye is somewhat weakened.

It is noteworthy that the full range of ocular movement is rarely employed, so that an operation which slightly limits the movement of the two eyes in certain directions produces relatively little handicap compared with the great advantage of removing the diplopia.

In all 70 cases the visual axes were restored to parallelism in the primary position and a useful field of binocular fixation was also obtained. All patients were observed for at least nine months after operation, and in every case the postoperative result was maintained.

Cerebral nerve injuries—Third cerebral nerve palsy—The three cases of third cerebral nerve palsy were the most difficult to treat. Fortunately the third nerve is rarely affected and the lesion is usually incomplete. Since the affected eye shows both defective elevation and defective depression, any attempt to improve either movement will automatically make the other movement worse. Hence the main surgical adjustment must be directed to the unaffected eye with a view to limiting its power of elevation and depression and to making the movement of the two eyes more symmetrical. It is most important at the outset to explain to the patient that most of the operative treatment must be conducted on the unaffected eye. It is also important to explain that complete cure is impossible (unless the paresis is very slight).

The main operation in these three cases consisted of recession of the superior rectus muscle and of the inferior rectus muscle of the unaffected eye; in one case recession of the lateral rectus muscle also was done. It may be necessary subsequently to carry out a recession of the lateral rectus muscle of the affected eye and an operation for the correction of ptosis, but this was not required in this group of patients. The aim is to gain orthophoria or something approaching orthophoria in the primary position and in the lower part of the binocular field—the latter because ordinarily looking down is so much more important than looking up.

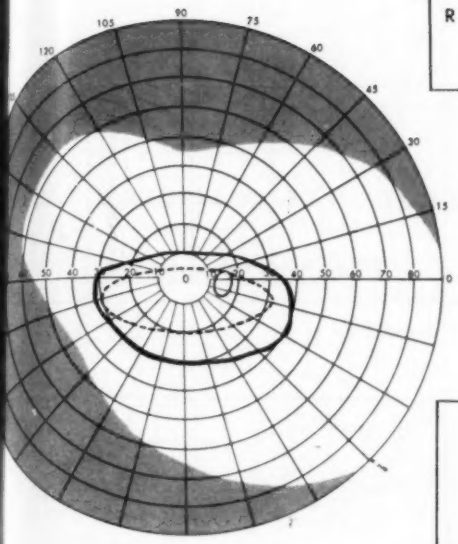
Figure 2 presents an example of surgical treatment of ocular palsy resulting from injury of the third cerebral nerve.

Fourth cerebral nerve palsy—Unilateral injury to the fourth cerebral nerve was the most common lesion, occurring in 23 cases. In these cases the prognosis is good, especially if the paralysis is incomplete. The choice of operation lies between weakening the direct antagonist, i.e., the ipsilateral inferior oblique muscle by myectomy or recession, and weakening the contralateral synergist, i.e., the contralateral inferior rectus muscle by recession or sometimes by marginal myotomy. Sometimes both procedures are indicated. On the whole it is preferable to deal with the direct antagonist first and then if necessary, a week or two later, to operate on the contralateral synergist. The advantage of this plan is that a myectomy of the inferior oblique muscle gives a certain maximal effect immediately and is not an operation that can be graduated, whereas recession of the inferior rectus muscle is a procedure that can be modified in extent according to the amount of deviation present. Thus by carrying out the surgical treatment in this order a more exact final result can be obtained.

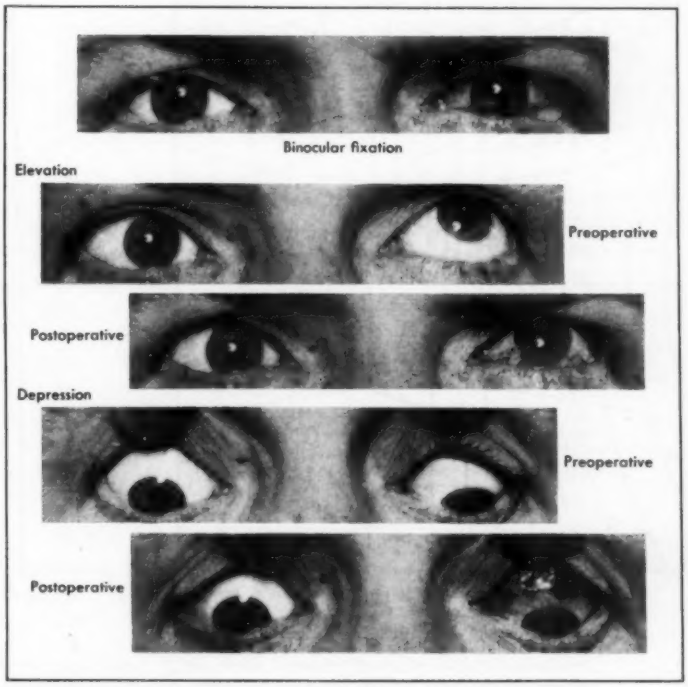
Table 3 lists the operative procedures that

L R	24△	21△	21△	17△	19△	20△ L R
L R	L)7△	7△	3△(R	L)4△	3△	2△(R L R
R L	2△	2△	4△	4△	4△	4△ R L
	Fixing with right eye			Fixing with left eye		

a. Major amblyoscope.



b. Field of binocular fixation. Broken line, before operation; solid line, after operation.

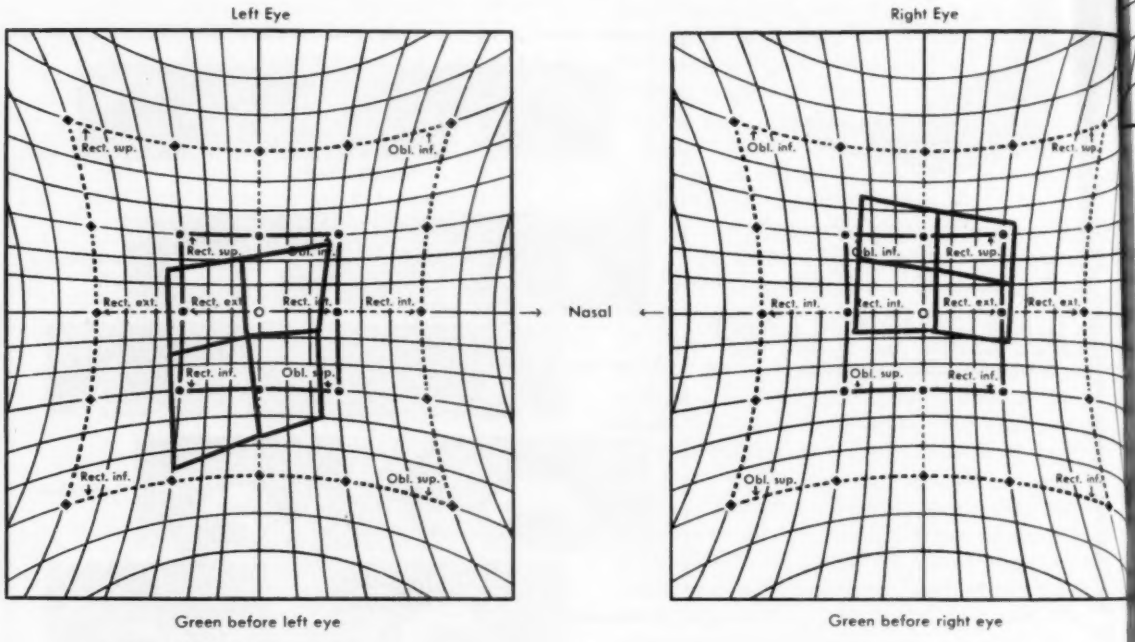


c. Improved appearance of eyes in elevation and depression after operation compared with preoperative appearance.

FIGURE 2. Ocular palsy due to injury of the third cerebral nerve. A 29 year old man collided head-on with a motor car while riding a bicycle and injured his head severely. The base of the skull was fractured. He was unconscious for three days. Five years elapsed between the time of injury and the operative treatment, during which he had constant vertical and horizontal diplopia. Maddox rod measurements, fixing with right eye, L/R 7△; fixing with left eye, L/R 3△. Gross weakness of elevation and depression, right eye. Operative treatment consisted of recession of the superior rectus and inferior rectus muscles of the left eye 5 mm. Postoperatively the Maddox rod test showed fixing with each eye R/L 1△. Ocular movements were much more symmetrical, and the field of binocular fixation was considerably increased.

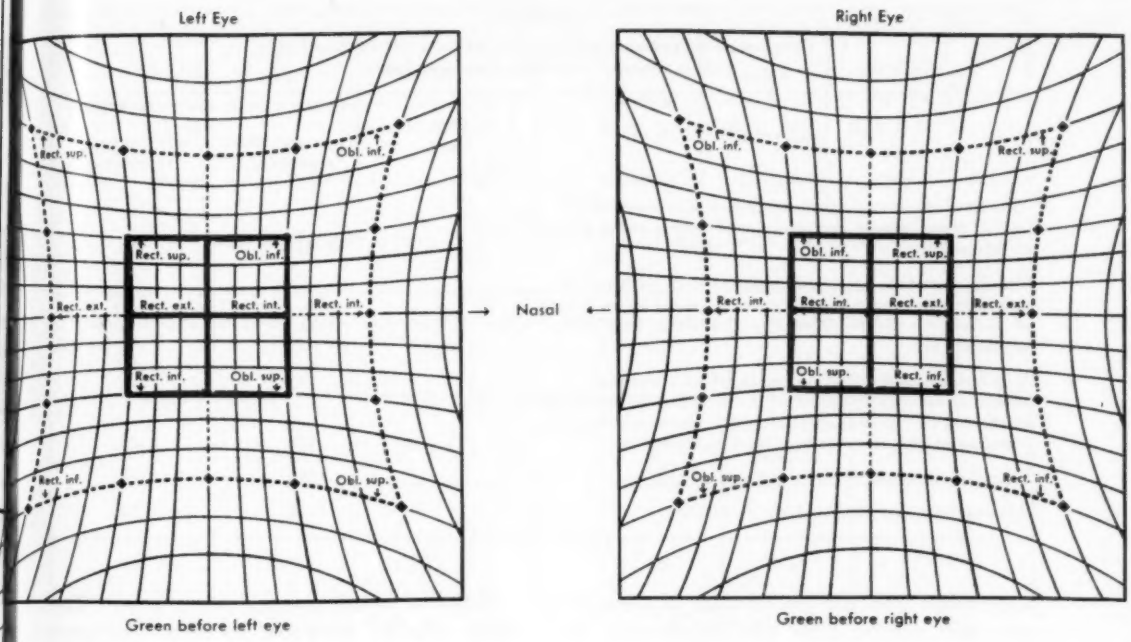
R/L 11Δ 0° L Exc 4°	R/L 9Δ −2° L Exc 4°	R/L 7Δ 0° L Exc 4°	R/L 10Δ 0° L Exc 4°	R/L 5Δ 0° L Exc 3°	R/L 25Δ 0° L Exc 3°
15° L	R/L 10Δ 0° L Exc 4°	15° R		R/L 9Δ 0° L Exc 2°	
R/L 26Δ 0° L Exc 8°	R/L 13Δ 0° L Exc 7°	R/L 11Δ 0° L Exc 7°	RL/ 18Δ 0° L Exc 8°	R/L 15Δ +2° L Exc 6°	R/L 18Δ +3° L Exc 7°
Fixing with right eye			Fixing with left eye		

a. Major amblyoscope. Fusion and stereopsis at 0° R/L 5Δ, range of fusion +20° to -5°.



b. Hess charts before operation.

FIGURE 3. Paralysis of fourth cerebral nerve due to head injury. A 25 year old man was hit on the right eye while boxing. In the nine months between the injury and the operative treatment he experienced vertical diplopia when looking straight ahead and to the left. Vision was 6/5, and N5 each eye. With the head tilted to the left shoulder and slightly turned to the left, he could gain binocular fixation for short periods. With the head straight, the right eye was moderately elevated and slightly divergent. There was updrift of the right eye on levoversion, with defective levodepression. The diplopia test showed vertical diplopia with maximal vertical separation of the images on levodepression, the distal image belonging to the right eye. Maddox rod measurement, at 6 meters, fixing with right eye, R/L 18Δ Eso 4Δ; fixing with left eye, R/L 18Δ Eso 2Δ. Operation was done 10 months after injury, and consisted of partial myectomy of the right inferior oblique and marginal myotomy of the left inferior rectus. Postoperatively there was binocular fixation in all positions of the gaze. Maddox rod measurement, at 6 meters, was Θ for each eye. Major amblyoscope, angle of deviation +3° R/L ½Δ.



c. Hess charts after operation.

were done in the 23 cases of fourth cerebral nerve palsy. Figure 3 summarizes a case representative of this group.

Sixth nerve palsy—In many of the 13 cases of sixth nerve palsy the nerve lesion was incomplete; thus the prognosis was accordingly fairly good. The surgical procedure was usually governed by the power of abduction of the affected eye. If the patient was able voluntarily to abduct his affected eye to the midline or just beyond, a muscle transplant operation was not thought necessary; the procedure then consisted of recession of the medial rectus muscle and resection of the lateral rectus muscle of the affected eye, and sometimes in addition a recession of the medial rectus muscle of the unaffected eye. If, however, the patient could not voluntarily abduct his affected eye to the midline, then a muscle transplant operation was deemed necessary. Slips

TABLE 3

OPERATIVE PROCEDURES AND RESULTS IN 23 CASES OF OCULAR PALSY DUE TO UNILATERAL INJURY OF FOURTH CEREBRAL NERVE

PROCEDURE	NUMBER OF CASES	AVERAGE MADDOX ROD MEASUREMENT	
		Before operation (hypertropia)	*After operation (hyperphoria)*
Ipsilateral inferior oblique myectomy	4	8Δ	½Δ
Contralateral inferior rectus recession	4	16Δ	1½Δ
Contralateral inferior rectus marginal myotomy	4	7Δ	½Δ
Ipsilateral inferior oblique myectomy and contralateral inferior rectus recession	11	13Δ	½Δ

TABLE 4

OPERATIVE PROCEDURES AND RESULTS IN 13 CASES OF OCULAR PALSY DUE TO INJURY OF SIXTH CEREBRAL NERVE

PROCEDURE	NUMBER OF CASES	AVERAGE MADDOX ROD MEASUREMENT	
		Before operation (esotropia)	*After operation (esophoria)*
Muscle transplant operation combined with recession of medial rectus muscle and resection of lateral rectus muscle of affected eye	7	37△	3△
Muscle transplant operation combined with recession of medial rectus muscle and resection of lateral rectus muscle of affected eye and recession of medial rectus muscle of unaffected eye	3	43△	5△
Muscle transplant operation combined with recession of medial rectus muscle and resection of lateral rectus muscle of affected eye and recession of medial rectus muscle and resection of lateral rectus muscle of unaffected eye	1	48△	2△
Recession of medial rectus muscle of affected eye	1	21△	4△
Bilateral recession of medial rectus muscle	1	16△	2△

were taken from the medial third of the superior and inferior recti and attached to the lateral rectus insertion.

The operations performed in these 13 cases are shown in table 4. Figure 4 is a summary of an illustrative case.

Third and fourth cerebral nerve palsies; third, fourth and sixth cerebral nerve palsies—These cases were the most difficult to treat because of combined weakness of elevation and depression in all directions of the gaze. It seems impossible to achieve much more than orthophoria in the primary position and a small field of binocular vision when looking slightly downward. The addition of a sixth nerve palsy to paralysis of the third and fourth nerves, with its resultant convergent deviation, limits the field of binocular fixation in the horizontal direction, although the restoration of orthophoria by operation is possible. The main surgical treatment usually consists of recession of the superior and inferior rectus muscles of the affected eye and recession of the lateral rectus muscle of the unaffected eye; and sometimes myectomy of the inferior oblique muscle and tenotomy of the superior oblique muscles. It is fortunate that, as in cases of unilateral third nerve palsy, paralysis is rarely complete.

Bilateral fourth cerebral nerve palsy—The chief difficulty presented by these two cases was the high degree of bilateral excyclotropia present due to contracture of the direct antagonists (inferior oblique muscles) and the overaction of the contralateral synergists (inferior rectus muscles). In one case, in order to overcome the tilting of the images, it was necessary to carry out not only a bilateral inferior oblique myectomy but also a recession of both inferior rectus muscles. In the other case, so great was the torsional deviation that a bilateral plication of the superior oblique muscles was carried out; but even then it was difficult to abolish the torsional deviation entirely except in the primary position or when looking directly up or down. Details of the second case are given in figure 5.

Bilateral sixth cerebral nerve palsy—These five patients needed treatment along the same lines as those with unilateral sixth cerebral nerve palsy. Bilateral muscle transplant may be required, or a muscle transplant on one eye and a simple recession of the medial rectus muscle and recession of the lateral rectus muscle on the other eye, depending on the circumstances. The operative procedures and results are given in table 5.

Orbital injury—Local injury to the orbit

15° L	10° L	Center
L/R 3Δ		
+39°	+42°	—

Fixing with right eye

15° L	Center	15° R
R/L 6Δ	R/L 3Δ	R/L 3Δ
+16°	+22°	+30°

Fixing with left eye

a. Major amblyoscope, before operation. Fusion at +30°; 4° abduction. Stereopsis with stimulation.

15° L	Center	15° R
	⊖	⊖
⊕	+3°	+20°

Fixing with right eye

15° L	Center	15° R
	⊖	⊖
⊕	+4°	+10°

Fixing with left eye

b. Major amblyoscope, after operation. Fusion and stereopsis at +3 ⊖. Range of fusion +9° to −1°.

FIGURE 4. Paralysis of sixth cerebral nerve due to head injury. A 40 year old woman injured in a motor car crash had a severe concussion and was unconscious for 10 days. Twenty months elapsed between the injury and the operative treatment of ocular palsy, during which time she had constant diplopia at first but learned to suppress the vision of her right eye to some extent. Vision was 6/6, and J1 each eye. The right eye was markedly convergent. There was paralysis of the right lateral rectus muscle. The right eye could not be abducted as far as the midline. At operation, almost two years after injury, a muscle transplant was done combined with recession of the medial rectus muscle and resection of the lateral rectus. As a result, the patient had binocular fixation in the primary position and to the left. Maddox rod test, fixing with right eye, Exo 2Δ ⊖; fixing with left eye, Exo 3Δ ⊖. Maddox wing test, Exo 4Δ ⊖.

TABLE 5

OPERATIVE PROCEDURES AND RESULTS IN FIVE CASES OF BILATERAL SIXTH CEREBRAL NERVE PALSY

PROCEDURE	NUMBER OF CASES	MADDOX ROD MEASUREMENT	
		Before operation (esotropia)	*After operation (esophoria)*
Bilateral muscle transplant operation with recession of medial rectus and resection of lateral rectus muscles (two stages)	1	100Δ	4Δ
Unilateral muscle transplant operation with recession of medial rectus muscle and resection of lateral rectus muscle, and recession of medial rectus and resection of lateral rectus of the other (less affected) eye	2	48Δ and 51Δ	2Δ and 10Δ
Unilateral recession of medial rectus muscle and resection of lateral rectus muscle	1	32Δ	⊖
Unilateral recession of medial rectus muscle	1	13Δ	2Δ

15° L	Center	15° R
R/L 1Δ	R/L 1Δ	⊖
Exc 10°	Exc 10°	Exc 10°

Fixing with right eye

15° L	Center	15° R
R/L 7Δ	R/L 4Δ	R/L 3Δ
Exc 15°	Exc 10°	Exc 15°

Fixing with left eye

a. Major amblyoscope, before operative treatment.

R/L 1Δ	R/L 1Δ	R/L 1Δ
L/R 1Δ	L/R 1Δ	L/R 1Δ
Exc 9°	Exc 9°	Exc 9°
R/L 2Δ	L/R 1Δ	L/R 4Δ
Exc 26°	Exc 21°	Exc 26°

Fixing with right eye

⊕	⊕	⊕
L/R 2Δ	L/R 2Δ	L/R 2Δ
Exc 7°	Exc 7°	Exc 7°
R/L 3Δ	⊖	L/R 2Δ
Exc 32°	Exc 32°	Exc 27°

Fixing with left eye

b. Major amblyoscope, after first stage of operative treatment.

R/L 4Δ		R/L 4Δ
Exc 3°		Exc 4°
	L/R 3Δ	
	No cyclo	
L/R 4Δ	⊕	⊕
Exc 7°	No cyclo	Exc 12°

Fixing with right eye

R/L 4Δ		R/L 4Δ
No cyclo		No cyclo
	L/R 3Δ	
	No cyclo	
L/R 3Δ	⊕	L/R 5Δ
Exc 7°	No cyclo	Exc 5°

Fixing with left eye

c. Major amblyoscope after second operation. Fusion at 0 with good fusional range and stereoscopic vision.

FIGURE 5. Bilateral fourth cerebral nerve palsy. A 38 year old man was unconscious for three weeks after injury in a motor car accident. He had a severe head injury. He experienced double vision when looking down or to either side, the images being tilted and also vertically separated. Two years elapsed between the injury and operative treatment. Maddox wing test, R/L 13Δ, Exc 12°. Diplopia test, vertical and torsional deviation greatest on levodepression. Myectomy of the right inferior oblique was done, and as a result the vertical deviation was reduced to nil, and torsional deviation was reduced by 3°. Two years later, bilateral plication of the superior oblique muscles was done. When the patient was seen two years after this second operation, he had much less diplopia. At that time, he saw double only when looking beyond 30° downward. He has continued his work as a draftsman. Maddox rod test, at 6 meters, Eso 2Δ L/R 2Δ, no cyclo. Maddox wing test, L/R 2Δ, Exc 4°.

may cause (1) fracture of the walls of the orbit, (2) damage to the suspensory ligament of the eyeball, (3) hemorrhage into the orbital tissues including the extrinsic ocular muscles, and (4) direct damage to the extrinsic ocular muscles, especially those with anterior attachments to the rim of the orbit, i.e., the superior and inferior oblique muscles. The orbital damage usually appears to cause a slight displacement of the position of the eyeball so that its visual axis becomes deviated and is directed slightly upward (hypertropia) or slightly downward (hypotropia)—and sometimes slightly inward or outward. In the former instance there is an accompanying defect of depression, and in the latter a defect of elevation. These defects of movement are usually relative rather than absolute and are not necessarily due to a defect of the muscles themselves or their nerve supply; rather they are due to the fact that the muscles concerned are acting at a mechanical disadvantage because of malposition of the eyeball. It is rarely possible to restore the position of the eyeball to normal by any direct means, although in certain cases some improvement may result from levering up a depressed orbital floor or by raising its level by a bone or cartilage graft. Such methods were not employed in this group of cases initially either because the patients were not seen early enough after their injuries or because improvement thereby seemed unlikely.

Defective elevation—In these cases, since there is usually no true defect of the muscles themselves or of their nerve supply, the operation of choice appears to be resection of the muscle whose main action seems to be relatively defective. For instance, in a defect of elevation a superior rectus resection is indicated. On the other hand, as an additional or alternative procedure an operation designed to weaken elevation of the other eye may give a satisfactory result. Sometimes a small recession of the inferior rectus muscle of the affected eye is indicated. The operations performed in the 15 cases of defective elevation resulting from ocular injury are listed in table 6. Figure 6 summarizes an illustrative case.

Defective depression—The main operation in these three cases was a resection of the inferior rectus muscle of the affected eye, but operation may also include either a recession of the superior rectus muscle or myectomy of the inferior oblique muscle of the affected eye, or recession of the inferior rectus muscle of the unaffected eye. Table 7 shows the operations performed.

Defective elevation and abduction—In the one case of defective elevation and abduction. recession of the inferior rectus muscle and of the medial rectus muscle of the affected eye was carried out. The preoperative Maddox rod

TABLE 6

OPERATIONS PERFORMED IN 15 CASES OF DEFECTIVE ELEVATION RESULTING FROM OCULAR INJURY*

OPERATIONS	NUMBER OF CASES
Resection of superior rectus muscle of affected eye	4
Resection of superior rectus muscle of affected eye and myectomy of inferior oblique of unaffected eye	3
Resection of superior rectus muscle of affected eye and recession of superior rectus of unaffected eye	1
Recession of inferior rectus muscle of affected eye	2
Recession of inferior rectus muscle of affected eye and myectomy of inferior oblique of unaffected eye	3
Recession of superior rectus muscle of unaffected eye	2

*Average Maddox rod measurement preoperatively, 13△ of hypotropia; postoperatively 1△ of hypophoria.

TABLE 7

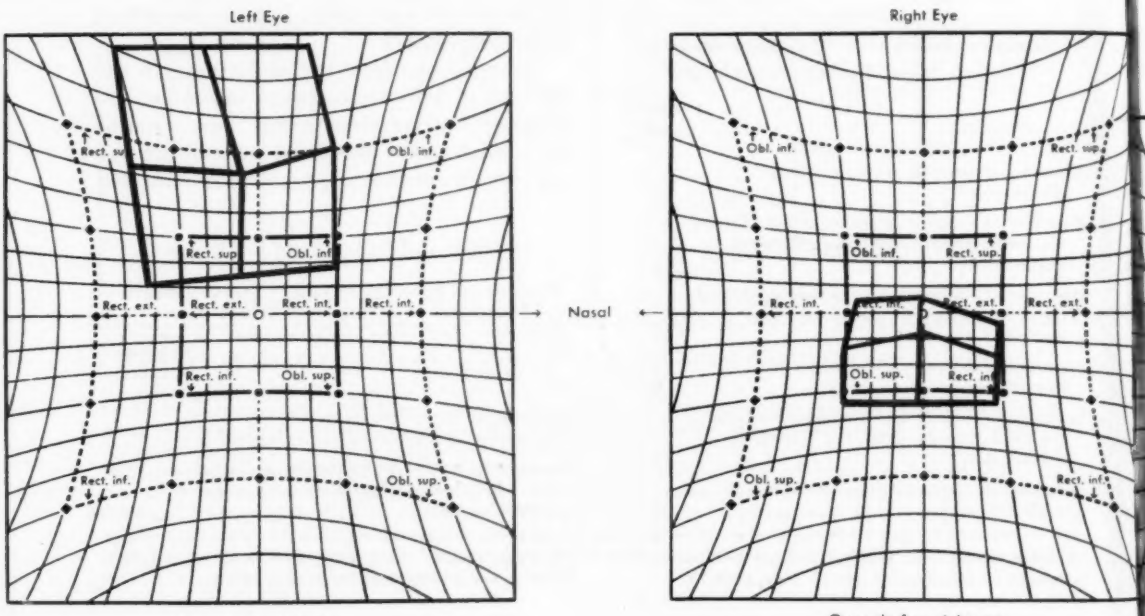
OPERATIONS PERFORMED IN THREE CASES OF DEFECTIVE DEPRESSION RESULTING FROM OCULAR INJURY*

OPERATIONS	NUMBER OF CASES
Resection of inferior rectus muscle and myectomy of inferior oblique of affected eye	1
Resection of inferior rectus muscle of affected eye, and recession of inferior rectus muscle of unaffected eye	2

*Average Maddox rod measurement preoperatively, 23△, hypertropia; postoperatively, 2△, hyperphoria.

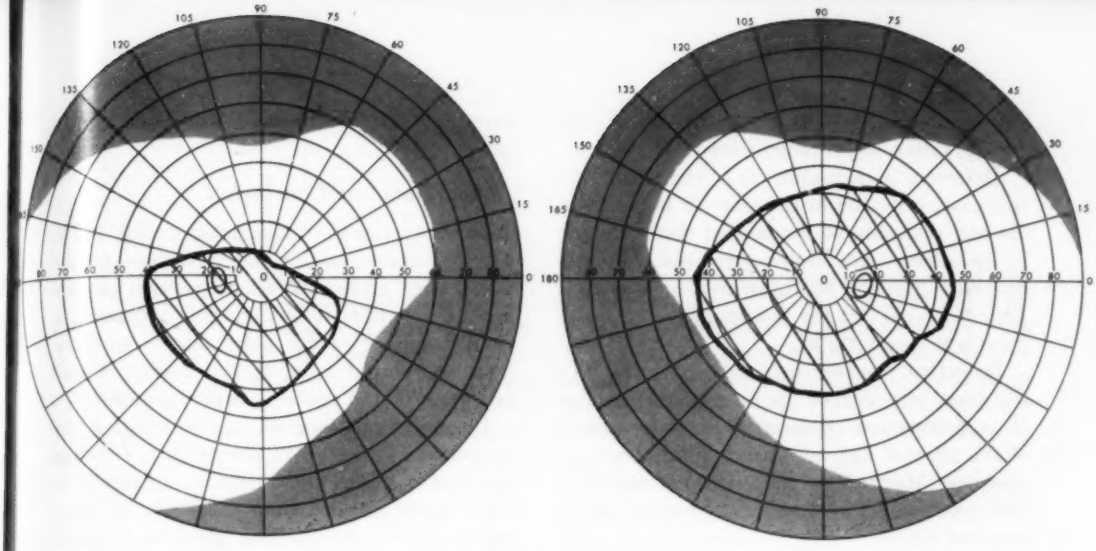
a. Compensatory head posture.

b. Defective elevation of right eye and right partial ptosis.



c. Hess charts before operation.

FIGURE 6. Defective elevation resulting from ocular injury. A 36 year old man was thrown through the windshield of a car in an accident. His skull was fractured and he had a wound over the right eyebrow. He was unconscious for 10 days. The right upper eyelid was closed for two months because of swelling of the tissues and also some weakness of the levator palpebrae superioris muscles. Thereafter the patient experienced vertical diplopia, except on extreme depression. Vision was 6/5, and N5 each eye. Elevation of the chin rendered the visual axes parallel. With the head straight, the left eye was markedly elevated and exotropic when fixing with the left. There was slight right ptosis. On ocular movement there was a marked defect of elevation of the right eye. The diplopia test showed vertical diplopia with slight horizontal component in all positions of the gaze, images most widely separated vertically on dextro-elevation and fused on depression, the distal image in each instance belonging to the left eye. Maddox rod test, at 6 meters, fixing with right eye L/R 14Δ; fixing with left eye L/R 18Δ. Subjective amblyoscopic measurement in primary position, fixing with right eye –11° L/R 32Δ; fixing with left eye –8° L/R 30Δ. Vertical deviation increased on elevation and decreased on depression. Fusion and stereopsis were good. Operation three months after the accident consisted of resection of the right superior rectus muscle 3.5 mm., recession of the left superior rectus muscle 2 mm., re-recession of the left superior rectus 2 mm., and recession of the left inferior rectus muscle 2 mm. As a result, the patient had binocular fixation in primary position with the head straight and when looking up. Maddox rod test, at 6 meters, Eso 1Δ Θ. Major amblyoscope, angle of deviation 0° R/L 1Δ. Hess chart normal, and field of binocular fixation much enlarged. Four months after the accident, Blaskovicz's operation was done for partial right ptosis.



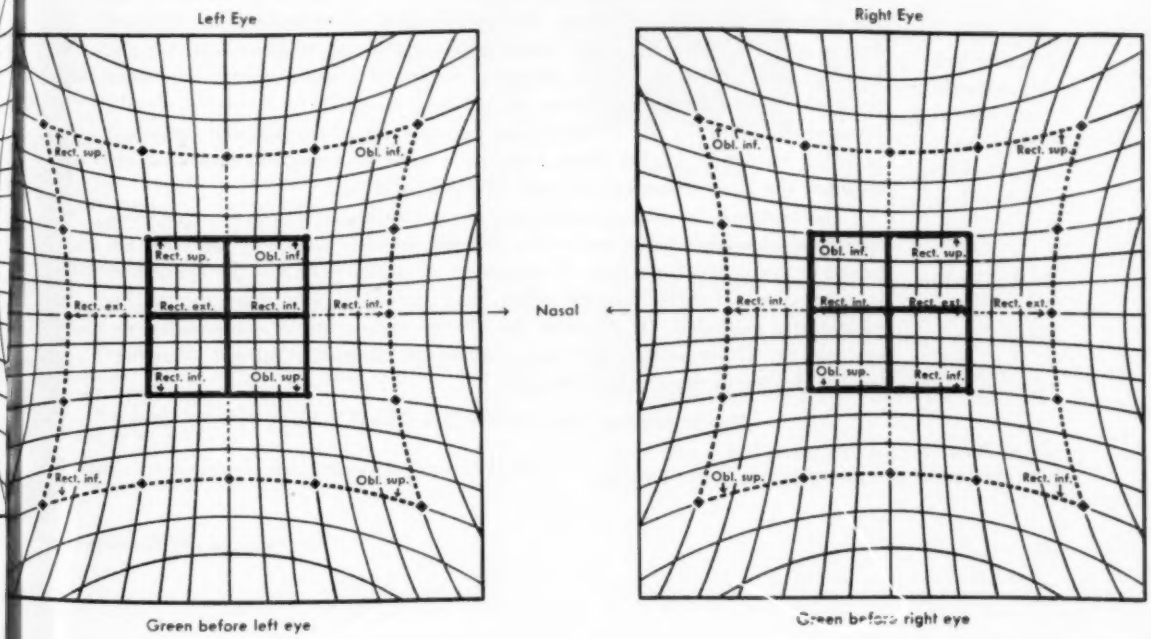
d. Field of binocular fixation before operation (left) and after operation (right).

e. Binocular fixation in primary position after operation.

f. Binocular fixation on elevation following the operation.

g. Final result after operation for right partial ptosis.

h. Postoperative Hess charts.



measurement was R/L 25$^{\Delta}$, esotropia 7$^{\Delta}$; the postoperative measurement was R/L ½$^{\Delta}$ Φ.

Defective depression and abduction—In this case, resection of the inferior rectus muscle and recession of the medial rectus muscle of the affected eye were carried out. The preoperative Maddox rod measurement was L/R 18$^{\Delta}$, esotropia 8$^{\Delta}$; the postoperative measurement was esophoria 2$^{\Delta}$.

Defective depression and adduction—In this case, resection of the inferior rectus muscle and resection of the medial rectus muscle of the affected eye were carried out. The preoperative Maddox rod measurement was R/L 14$^{\Delta}$, exotropia 21$^{\Delta}$; the postoperative measurement was Φ.

Defective adduction—Resection of the medial rectus muscle was done in this case. The preoperative Maddox rod measurement was exotropia 15$^{\Delta}$; the postoperative measurement was Φ.

Summary and Conclusion

In most cases of traumatic ocular palsy, surgical correction of the deviation of the visual axes gives satisfactory results, but operation may have to be done in several stages. In 70 cases of ocular palsy due to head injury, substantial relief of symptoms followed operation on the extrinsic ocular muscles.

In unilateral cerebral nerve injuries the prognosis with regard to normality of function was best in fourth nerve palsies, quite good in sixth nerve palsies, and only fair in third nerve palsies. It was less good in bilateral injuries and when more than one nerve was affected. The prognosis was very good in cases of relative ocular palsy due to orbital trauma.

Postgraduate Clinical NOTES

106. DIAGNOSIS OF ANGINA PECTORIS

The recognition of angina pectoris depends essentially upon the patient's ability to describe his subjective sensation and the physician's ability to evaluate the situation. Mostly the diagnosis can be made with assurance on the history. The language of sign and gesture is of great value. The clenched fists across the chest, the open hands gripping the side of the chest, a right hand gripping the left wrist or biceps are often of greater significance than the spoken word. Direct questions, albeit posed obliquely or inversely, should be used and certainly not avoided. Few patients talk of other symptoms when giving a history of angina; their concern is with the one pain. Most will remember the circumstances and time of the first attack.

The response to nitroglycerin may be misleading, for the drug relieves spasm of smooth muscle generally and psychoneurotics may also be relieved of symptoms for a time. A diagnosis of angina pectoris, the symptom, is insufficient; cardiac causes other than coronary atheroma should be sought and excluded. In all cases the electrocardiogram is a necessary investigation. Abnormalities not only confirm the diagnosis but aid in assessing the degree of myocardial damage.

Wallace Brigden, Angina pectoris, *Practitioner*, February 1958, pp. 167-171

Epilepsy without demonstrable cause may begin at any age. Hereditary predisposition; prenatal infections; possibly, radiography of the pelvis during pregnancy; congenital defects; and cerebral lesions acquired during or after birth are some of the causal factors. Investigative procedures include electroencephalography, radiography, pneumoencephalography, angiography and lumbar puncture. Operation should be considered only in severe cases after medical treatment has failed. Patients should be encouraged to live as normally as possible.

A Perspective of Epilepsy

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THE dramatic nature of the epileptic seizure ensured its early recording. One of the most vivid accounts is to be found in the Bible (St. Mark 9:17-26).

And one of the multitude answered and said, Master, I have brought unto thee my son, which hath a dumb spirit;

And wheresoever he taketh him, he teareth him: and he foameth, and gnasheth with his teeth, and pineth away. . . .

And they brought him unto him: and when he saw him, straightway the spirit tare him; and he fell on the ground, and wallowed foaming.

And he asked his father, How long is it ago since this came unto him? And he said, Of a child.

And ofttimes it hath cast him into the fire, and into the waters, to destroy him: but if thou canst do any thing, have compassion on us, and help us. . . .

. . . he rebuked the foul spirit, saying unto him, Thou *dumb and deaf spirit, I charge thee, come out of him, and enter no more into him.*

And the spirit *cried, and rent him sore, and came out of him: and he was as one dead; insomuch that many said, He is dead.*

But Jesus took him by the hand, and lifted him up; and he arose.

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E. GRAEME ROBERTSON

Definition

John Hughlings Jackson's definition of epilepsy remains as satisfactory as any made since: "The paroxysm is dependent upon a sudden temporary, excessive, disorderly discharge of some highly unstable region of the cerebral cortex."

A Practical Approach

In our present stage of incomplete knowledge it is difficult to classify the many epileptic manifestations. Hence it is reasonable to begin by analyzing the stages of the physician's reasoning when he deals with an epileptic patient.

1. First a full description of attacks is obtained from the patient and eyewitnesses and

the significance of other symptoms and physical signs is assessed.

2. Then the physician considers the nature of the attack, whether or not it is epileptic, and, if so, of what type.

3. Next he analyzes, in the light of present knowledge, the scientific implication of the type of attack. It is this which occupies most of the clinician's reading, and toward its solution goes an enormous amount of research.

4. What is the probable cause of the attack? Is the cause as yet unknown or can one or more of the underlying factors be guessed at or presumed? In particular, is a removable cause possible?

5. Is investigation desirable, or necessary, in the hope of obtaining further information that will be of benefit to the patient? In this way the small proportion to be subjected to surgical treatment may be sorted out.

6. If the conduct is to be medical, what treatment is to be prescribed and what adjustments (usually psychologic) are necessary in the patient's life?

What follows is an amplification of this analysis, directed toward achieving a practical solution for each patient. Since the age of the patient is of great importance, the presentation of subsequent sections will, where possible, be in terms of age.

Chronology of Onset

Gowers[1,2] in 1901 analyzed the age of onset in 3,002 cases of epilepsy, with no attempt to separate types, and reported the following percentages for the various age groups: under 10 years, 27.5 per cent; between 10 and 20, 46.5; 20 to 30, 15.5; between 30 and 40, 6; between 40 and 50, about 2.5; between 50 and 60, 1; over 60, 0.5.

> The number of cases is largest in the first year, and falls rapidly to three years of age, and then more slowly until five, when the minimum for the early period of life occurs. From this there is a considerable rise at seven, the commencement of the second dentition, then a fall at eight, and from this the numbers increase slowly at nine and 10, rapidly at 12, until the maximum is reached at 15 and 16, at which 166 and 167 cases commenced—about one-seventh of the total number. From this period we have a rapid fall to 21, after which only a small number began in each year.
>
> They will be found to fall, for the most part, into three classes: (1) Those in which labour was protracted and difficult, or (seldom) premature and swift, in which the symptoms immediately after birth suggest some meningeal hemorrhage. (2) Cases in which the attacks begin by a severe fit or series of fits, with indications of a local cerebral lesion. (3) Cases which constitute the majority, in which the infantile fits are at first slight, and are associated with retarded development, especially manifested by backward teething.[1]

This analysis seems to underestimate the percentage of cases of epilepsy beginning after the age of 40, with which the neurologist so frequently deals. He sees only a few of the cases occurring in young life, in which the attending physicians consider the condition "idiopathic" or refer patients to pediatricians.

Epilepsies of Early Life Associated With Cerebral Damage

Early epileptic manifestations are varied and often difficult to recognize. The earliest manifestations may occur soon after birth. Localized or irregular generalized twitching may last for hours, or generalized tonic attacks may occur, usually in association with other evidence of cerebral damage such as asphyxia, drowsiness, coma, rigidity and paralysis.

These manifestations clearly indicate severe cerebral damage due to mechanical or anoxic factors, and the possibility of a removable subdural hematoma must be kept in mind; in most instances the latter can be recognized by skillful tapping of the subdural space through the anterior fontanel. If the manifestations persist in a more chronic fashion it is still important to exclude subdural collections.

Early epileptic manifestations not due to subdural collections are very varied and may be so slight that they escape detection. The child may become pale, with some respiratory dysrhythmia, the eyes may roll upward, the child may stiffen, and minor twitching may occur. Consciousness may or may not be obviously disturbed. Occasionally the mother

notices phasic impairment of awareness which may be mistaken for drowsiness unless it proves impossible to arouse the child. This is often evidence of cerebral damage and these children not infrequently deteriorate mentally.

To convey a clear impression of this type of patient and illustrate the diversity of the clinical manifestations, the history of a two and one-half year old boy may be recounted in his mother's guided words:

> I understand that it was an entirely forceps birth. I was not allowed to unwrap him, but the doctor told me he was stiff, his head was inclined backward and his arms were stiffly by his side. Lumbar puncture was done at nine days; it was successful and fluid was drained. The stiffness improved subsequently but he slept very poorly.
>
> He seemed to be like a normal child to my husband and myself. He was our first child. We thought he recognized us. Six to 10 months was the worst period; he did not seem to make one bit of progress. At about six months he could sit when propped up.
>
> When about 12 months old his whole body began to tremble—becoming more severe in the afternoon and later when he was trying to do things. His eyes would occasionally have a staring effect if the tremor lasted for long. He usually dropped things during the turns and sometimes he whimpered. The slightest upset of health produced such tremors that he could hardly be handled.
>
> At 12 months he was able to sit up by himself. He picked up toys and seemed interested in them. He is still trying to pull himself into a standing position and has not succeeded. He cannot feed himself. He tries, but the shakes interfere. We think he understands what is said to him. He seems to recognize a lot of people. He does not say any words.
>
> Three months ago he had a slight convulsion which lasted about four minutes. About a month later he went very white and started to jerk a little. This stopped and then he became blue and started to choke a little. He then seemed to go into a deep sleep and would twitch occasionally, appearing at times to be about to come round. Then he had a severe convulsion lasting three to four minutes. There was no difference in the twitching on the two sides of the body.
>
> On two occasions he became limp and pale and seemed unconscious for three to four minutes. The second he opened his eyes again he seemed perfectly normal. The tremors have gone on all the time.
>
> Last month, from time to time, he has drawn his lips tightly across his teeth and screamed.

The child sat on his mother's knee grunting from time to time and uttering inarticulate sounds. Sometimes sudden forcible dorsiflexion of the trunk and head occurred, sometimes his mouth twitched and eyelids flickered while synchronously his arms jerked upward. His head might turn to one or the other side. The tremors which occurred many times an hour were minor forms of these attacks. He was able to stand and walk with bilateral support. Attempts at physical examination produced a succession of jerks that made estimation of motor functions difficult. However, there was no evidence of an upper motor neuron lesion. He was grossly retarded mentally.

In this group the electroencephalogram often shows continuous slow activity of varying rate and voltage (often high) with paroxysmal admixture of irregularly grouped multiple spikes and slow waves. I have believed that such abnormal interictal tracings suggest cerebral damage, perhaps associated with many causes and varying types of epileptic discharge.

Certain groups have been segregated on electroencephalographic grounds, and some of these patients may be classified into the same groups clinically. The subdivision has prognostic significance.

Hypsarhythmia (Gibbs and associates[3-6])—Clinically these patients have frequent convulsive episodes, jerking, quivering spells or spasms. There is cerebral underdevelopment, with a further deterioration. Electroencephalograms show continuous high voltage waves and spikes, diffuse and nonrhythmical. The condition usually begins in the first year of life and is only found in the first four years. After this time the pattern usually is replaced by a normal electroencephalogram or one with focal qualities. Major convulsions occur in one-third of the cases. Gibbs et al.[5] said, "the chief hazard of this condition is not epilepsy, but death (11 per cent die before the third

year) or feeble-mindedness (87 per cent become mentally deficient)." This group is important because of the mental deterioration which occurs. Such patients are poorly understood, chiefly because pathologic knowledge is fragmentary.

Slow wave and spike attacks or "petit mal variant"—In this group there are short attacks of staring, sudden sagging, head nodding, "salaam" spasms, falling, jerking, flexor or extensor stiffening limited to one or more limbs, dreamy states, and various degrees of impairment of consciousness. The child often shows evidence of cerebral hypoplasia. Electroencephalographically there are outbursts of two per second waves and spikes, often from a localized focus. In contradistinction to true petit mal the discharges are little affected by changes in carbon dioxide concentration. Often there is persistent evidence of structural damage, which is absent in true petit mal, while the electroencephalogram is less likely to become normal than in petit mal. The attacks are less amenable to treatment.

Epilepsy Due to Causes Acting Symmetrically on the Hemispheres

It is probable that structural damage exists in a high percentage of the cases described in the foregoing section. In the group now to be considered structural damage is less common. Indeed in petit mal there is little evidence of such damage. It is my belief that cerebral damage exists in a number of patients with grand mal, but certainty is lacking.

Petit mal—Petit mal is essentially a disease of children of school age. The attacks are well described by the word *absence* or lapse. Gowers[2] described them as follows: "The individual suddenly stops in his occupation, looks strange for a moment, and then goes on with what he is doing, may even finish a sentence that he has commenced, and be aware of what has happened only by finding that he has dropped something out of his hands, or that he is the object of anxious observation."

This type of attack is marked by the sudden eruption of rhythmical three per second spike and slow wave activity beginning synchronously over both hemispheres or in bilaterally symmetrical regions (usually frontal). The disorder has a strong tendency to cease toward the end of the second decade of life, but if major attacks occur, and they frequently do, they are prone to continue.

Even the purist realizes that some automatic motor activity may occur in such attacks and it is difficult to know where this class should end and others such as "minor motor attacks" (considered by Wilkins[7] and Budge[8] to be abortive convulsive, or major, attacks) begin. In these, consciousness is variably impaired, the child may or may not fall, and irregular tonic and clonic muscular activity of brief duration occurs. There are bursts of high voltage slow waves demonstrated in the electroencephalogram.

Grand mal—Grand mal may begin at any age, but the most common ages of onset are the first year and between the ages of 7 and 14. Its essential characteristic is immediate loss of consciousness with the synchronous onset and symmetrical distribution of motor manifestations, although not infrequently the head and eyes turn to one or the other side but not always to the same side.

Febrile convulsions—These occur between the ages of one and three years in association with some general bodily illness. Margaret Lennox[9] found that 52 of 153 children with febrile convulsions had recurrent convulsions without fever. She stated that "from both clinical and electroencephalographic evidence, febrile convulsions may presage recurrent idiopathic convulsions. This unfavourable outcome is more apt to occur in the presence of a history of an atypical age of onset (before one and after three), of frequent and severe convulsions with prolonged fever, of an abnormal birth or a family history of epilepsy or of convulsions on both sides of the family, and in the presence of an abnormal electroencephalogram. However, it must be recognized that the outcome may be unfavourable in the absence of any of these features."

However, Carey[10] questioned authoritative teaching and declared that the prognosis of febrile convulsions must be considered good, for only six patients of 100 who had febrile convulsions at least 10 years previously were

diagnosed as having epilepsy. Even this is not a negligible percentage. The importance of this point lies in the desirability of anticonvulsive treatment when more than one febrile attack has occurred.

Myoclonus epilepsy—Sometimes myoclonus epilepsy occurs alone but usually it occurs with major attacks. It consists of violent muscular jerks occurring usually bilaterally and synchronously in flexor muscles, usually in the arms, and when they occur in trunk and legs they may precipitate the patient to the ground. The jerks are frequently asymmetrical or unilateral, are most common in the early morning and often lead to a major convulsion.

Akinetic or drop attacks—More controversial are the akinetic or drop attacks in which the patient loses muscle tone and falls to the ground, getting up immediately. Electroencephalographers tend to deny the existence of such attacks, having failed to record an electroencephalographic counterpart and regarding them as myoclonic.

Self-precipitated photogenic epilepsy—This is a fascinating form of epilepsy occasionally seen in children and more rare in adults. The literature had very few brief references to some part of the syndrome before Bickford and co-workers[11, 11a] reported on the condition. Epileptic attacks are induced by rhythmical interruption of sunlight by waving the hand (often with abducted fingers) in front of the eyes or by rapid blinking. The act may be frequently repeated, the sun "acting as a sort of magnet" to which the patient will turn. Brief attacks usually result, with an electric counterpart of irregular high voltage spike and slow wave discharge, but occasionally, usually when the waving continues for some time, falling and major attacks are precipitated. The patient is unable to explain why he does it. Sometimes he admits to a certain satisfaction, and he continues to wave even though he is highly embarrassed by it. Drug therapy is useless. Inducing the patient to try to refrain from the hand waving and to wear dark glasses and a broad-brimmed hat when in sunshine is the most effective therapeutic measure, but few will carry it out. The attacks can be reproduced by an intermittent photic stimulation during an electroencephalographic recording.

Petit mal, grand mal, and akinetic and myoclonus epilepsy have long been called idiopathic to indicate that the conditions are diseases in themselves, that known or detectable causes do not exist (obviously varying according to the degree to which investigation is carried), or, by some, to connote that removable causes do not exist, which is a different matter. Droogleever-Fortuyn, Jasper and Penfield[12-14] were largely responsible for the concept of a centrencephalic origin for such attacks showing bilaterally synchronous electric abnormality, so that the term "centrencephalic" replaced the term "idiopathic." John Hughlings Jackson conceived of the whole cortex being affected by the epileptogenic process; the new theory, with a good deal of physiologic and electroencephalographic support, suggested that central pacemaking cells could fire off to the cortex on both sides, and when abnormal produce generalized dysrhythmias. Some doubts of the validity of this concept are now being voiced, and it may be that the attacks do not start in this central region but are generalized through it. Droogleever-Fortuyn[12] concluded a recent paper with the significant sentence, "It may well be that the di-mesencephalic junction maintains its central place as a linkage between the two hemispheres." The huge body of the corpus callosum, a neglected but very large commissure, may play a part in generalization, or it may be that, as Jackson had in mind, some chemical cause fires off the whole cortex.

Focal Epilepsy

In contrast to the group just described are attacks due to focal cortical discharges, as was first recognized by John Hughlings Jackson. He believed that the abnormal discharge might remain localized to the area where it started and produce, in perverted form (since the excitation is abnormal), symptoms resembling the normal activity of the part. In some cases the excitation would spread in terms of the cortical arrangement of neurons, producing the types of motor and sensory attacks which bear Jackson's name.

The electroencephalographer's concept is

that focal attacks are due to the stimulation of part of a thalamocortical system extending from the cortex to the thalamus, which may be fired off from either end, most frequently from the cortical end. Thus they differ from the centrencephalic or generalized attacks which involve central firing to both sides, although even this might be triggered from the cortical end of these "systems in depth."

Such attacks are often called symptomatic to differentiate them from those without a detectable cause, but this is unwise since epilepsy is always a symptom whose cause is often unknown. Focal attacks are more common in adults than in children, although the electroencephalographic equivalent (focal spikes) is not uncommon in children, even in the absence of focal attacks. It may be difficult to obtain a sufficiently detailed history to recognize such attacks in children.

Uncinate epilepsy—There are many types of focal attacks, depending on the cortical area stimulated. Jackson demonstrated a lesion of the uncus in a patient who had "dreamy states" and olfactory hallucinations. He believed that a paroxysm of the underlying substratum of the sense of smell was just as much an epilepsy as is a motor fit. Thus the term "uncinate epilepsy" arose. Gowers well described these attacks with "turning inwardness of consciousness" which are now called temporal lobe or psychomotor epilepsy. These attacks are among the most fascinating of all epileptic manifestations. They test the art of the historian and have infinite variability from patient to patient. In spite of this they have a common characteristic of an unusual or unnatural experience of which the patient is aware. He may recognize it as being very familiar and having occurred before, but when the attack is over he is unable to find words to do it justice or to remember the exact qualities of the experience. Frequently the patient says something like this: "Someone I knew said something to me which he had said many times before, but when it was all over I could not for the life of me remember who it was or what was said."

In order that a patient's tentative description of such bizarre experiences may not be brushed aside, some examples may be cited.

A boy of seven years inadvertently injured his cat. He was very upset, and a short time later came to his mother saying that he could hear talking. He insisted that one voice was his brother's. Then he started to shout at his mother, and apparently he could not hear what she said for he shouted, "Why don't you answer?" He seemed to become exasperated and his speech was muddled and thick. For some minutes he kept asking whether the cat was dead. On another occasion he came into his parents' bed and told his father that he smelled, and later he said that his mother's arm smelled. About half an hour later he heard his brother's rather measured tread on the floor of the room above. He looked up and then seemed to be staring into space and took no notice of what was said to him. He then insisted on going upstairs to look in the room above, and when he came down his speech was thick for a short time.

For six months, a 16 year old boy had at times experienced "something which seemed to be started by a noise or vibration, which set up a feeling in my head. It sounded as if people were talking and shouting at me. I could hear half of what they said—just enough to stop me concentrating on anything else, although I try to turn my mind elsewhere. It seems to be people that I know around me, but I can't actually say who they are. Sometimes all sorts of noises that I can't identify seem to fill my head and irritate me and blot out everything else. Sometimes it seems to be what was said by someone before that strikes my mind. I think, Oh, I've heard that before. If anyone talks to me I can hear and I think I understand. I know I should answer, but I can't concentrate and say it and I can't speak." The noise of a bus starting, a chance puncture of a tire of a passing car, a plane flying overhead, a train going past while he was playing cricket, a big petrol motor starting—all have precipitated attacks.

A boy of 15 said that one day the noise he was making moving about the room seemed distorted. After about 10 seconds he blacked out and apparently had a generalized convulsion. Five months before, the sound of the wireless, a song with a steady beat, seemed to pound in his head. He could not say whether it went away or whether the song stopped. Between the ages of 8 and 13 years he had noticed that when he was thinking and saying something over and over *in his mind,* or aloud, the word or sentence would

take on the wrong sound. It did not seem to sound the same as when he first thought of it.

A man of 34 years gave the following account: "Twelve months ago while driving for about four hours along the river I got the sudden desire to drive under some willow trees by the side of the road, and I remember thinking I must be going silly. A mellow sort of music came into my mind, and a clergyman too—someone I knew in the past. He just seemed to be there, but it was probably not visual or formulated. I talked to myself—that I must pull up. I let the car come to a stop and lay under the willows about half an hour, and then I was all right. Later, when similar sensations occurred when others were present, I was told that I mumbled about something quite different from what we had been talking about. After the attacks I cannot remember what the music is like, except that it is soft. I used to know a clergyman who played the mouth organ, but I cannot say whether it was him or the music his. About nine weeks later I came to one morning to find the doctor in the room and I was told that I had had a fit. I had bitten my tongue. I was told that I had frothed at the mouth, breathed deeply and seemed to be chewing something."

A 28 year old man described his attacks as follows: "In the attack I start to get a smell which I can't describe. It is a queer smell—the more I try to work it out the further I am from it. It gets worse and worse and I lose the feeling in my feet. If driving my car I have to push the accelerator down to feel I'm doing it. The smell may sometimes go away, or I may lose consciousness. In one attack the smell came on and I heard a knocking at the back of my head. It seemed to be in the room with me, as if someone in the room was knocking at my head. I clutched at the back of the couch and it stopped. Most of my attacks occur when I'm driving my truck and I stop it now as soon as I notice a smell, but I've had two smashes."

Such descriptions are fascinating, and an enormous variety could be quoted. Few show the presence of a single hallucination (smell most commonly occurring alone); rather there is an intermixture of phenomena. These attacks are due to epileptic discharges beginning in the pararhinal area of the posterior part of the inferior surface of the frontal pole and the anterior part of the temporal lobe. Sclerosis has been demonstrated in some of these areas, and Penfield has suggested that

TABLE 1

SEIZURES OF EPILEPSY
GASTAUT'S CLASSIFICATION

1. Sensory symptoms
   a. Somatosensory seizures (parietal lobe)
      (1) Exteroceptive symptoms
      (2) Proprioceptive symptoms—a feeling of abnormal position or displacement of a limb
   b. Visual seizures (striate and parastriate areas)
   c. Auditory seizures (superior temporal gyrus)
   d. Vertiginous seizures (first temporal convolution)
   e. Olfactory seizures (anterodorsal part of uncus)
   f. Gustatory seizures (superior lip of operculum)
2. Psychic seizures
   a. Illusions, déjà vu, incongruity, unreality, familiarity (temporal lobe)
   b. Hallucinations—complex scenes (temporal lobe)
   c. Loss and clouding of consciousness, compulsive ideas (temporal and frontal lobes)
   d. Affective phenomena, commonly fear
3. Motor seizures
   a. Clonic seizures (motor cortex)
   b. Tonic and atonic local seizures
   c. Versive seizures, adversive movements of head and eyes to one side, or complete rotation of body (posterior part of inferior frontal convolution)
4. Automatisms
   a. Continuation of movement before the attack
   b. Movements as part of the fit, often the same from attack to attack, commonly undressing
   c. Alimentary automatisms
   d. Mimetic automatisms—expressions of the abnormal affective state
   e. General—directed to self or environment, fighting when an attempt is made to restrain automatic activity
   f. Ambulatory
   g. Verbal
5. Loss of articulation (Broca's area)
6. Aphasic seizures (temporal lobe)
7. Visceral symptoms, movements of oral end with salivation, epigastric aura, suffocation, tachycardia
8. Autonomic seizures—pallor, flushing, sweating

pressure and ischemia due to compression of brain tissue or arteries against the sphenoidal ridge and free edge of the tentorium at birth or during head injuries account for many of these epilepsies. It may be difficult to detect the abnormal electric discharges without using special technics.

Focal epileptic manifestations—Gastaut's[15] classification (table 1) of the "seizures of partial epilepsy" admirably summarizes the matter; the anatomic sites are in parentheses.

Bad behavior may occur in epileptic patients between attacks for a number of reasons, including defective cerebral control due

to hypoplasia, subclinical dysrhythmias, drugs (e.g., phenobarbital in the young may produce irritability) and psychologic factors. Sometimes abnormal behavior is ictal, i.e., due to a focal attack, and sometimes the only evidence of epilepsy may be the electroencephalographic record.

Some Causal Factors

It is impossible to deal with all etiologic factors, but some points that bear on questions of investigation need mention. It is reasonable to believe that individuals vary in their proneness to convulse. If the immediate stimulation is sufficiently strong, any person may convulse, but the stimuli which occur clinically produce convulsions only in the more prone individuals. The belief that the cerebral mechanisms involved are unstable has inspired the statement that man is built to convulse, variations depending on different capacities to inhibit the spread of explosive excitation.

Hereditary predisposition—The tendency to convulse may be an inherited quality. It is difficult to estimate the importance of genetic factors in epilepsy, but electroencephalographic recordings of relatives of epileptic persons and the study of epileptic twins have produced definite evidence of this hereditary predisposition. Lennox[9] contrasted the incidence of fits in 43 monozygotic and 23 dizygotic twins, one or both of whom had epilepsy. In 83 per cent, both monozygotic twins without brain injury had epilepsy; the incidence of epilepsy among those with brain injury was 16 per cent. Both dizygotic twins without brain injury were affected in 6 per cent, and with injury none. Statistical study suggested that constitutional endowment or predisposition and acquired gross pathology of the brain were forces roughly equal in strength.

Causes active in utero—The first damaging agent to be recognized, *Treponema pallidum*, is now a rare cause of fetal involvement. Only recently has the importance of other prenatal infections become recognized, chiefly due to work on rubella and toxoplasmosis. It is probable that other viral infections may affect the fetus. Viral pneumonitis, hepatitis and other infectious disease may all contribute. Indeed, many parental illnesses may not be without influence. Effects of radioactivity have been studied, and even medical radiography may not be without influence, especially if applied to the pelvis during pregnancy.

Congenital defects—The experimental work of Ingalls[16] has shown that hypoxia impairs the development of those parts of the embryo which are undergoing particularly rapid changes at the time of the stress. Thus stresses applied at the same stage of development produce the same results. This explains those associations of congenital lesions which have seemed so mysterious. Ingalls[16] asserted that "the implication of all that is known of maternal rubella, syphilis, toxoplasmosis and influenza; the effects of thiouracil, lead or carbon monoxide poisoning during pregnancy; of diabetic, haematological, circulatory and dietary disturbances; and of traumatic radiation and hypoxic diseases of the mother, placenta and embryo is that many, if not most, congenital anomalies will be eventually brought under control as appropriate scientific studies clarify causes." This may well have an application to epilepsy. While major damage produces localized or generalized cerebral underdevelopment with epilepsy, minor cerebral damage due to hypoxia or other maternal stresses may lead to epilepsy with normal mentality.

Postmaturity with diminution of the placental circulation may produce hypoxic cerebral changes. Prematurity may render the brain more vulnerable to noxious agents, including hypoxia and trauma.

Cerebral damage at birth—Although incompletely analyzed clinical material, or too few cases, may produce fallacious impressions, my experience in a large children's hospital, amplified by pneumoencephalographic study, has convinced me that cerebral damage at birth due to mechanical trauma or hypoxia is a potent factor in causation of epilepsy. It may be impossible to alter some causes, e.g., difficult and prolonged labor due to various factors such as disproportion and abnormal presentations, difficult delivery with forceps, the umbilical cord twisted around the neck, unduly rapid labor, and inhalation of meconium.

Happily the proportion of difficult labors is small, but damage does occur in a small proportion of labors and in some instances is avoidable. To minimize danger, the conduct of labor should be in skilled hands or at least in unhurried hands. There is a curious lack of discussion of this point in neurologic and obstetric literature. Unskilled and unnecessary use of forceps may well increase the morbidity, while skilled use may avoid damage. A nurse's holding back of the head until the doctor arrives is surely to be condemned. The vulnerable brain is compressed and its circulation impaired by forces acting above and below. Trial of labor resulting in "failed forceps" is surely most deleterious, however rapidly and skillfully the subsequent cesarean section is performed.

Courville[17] has strongly favored this thesis and Penfield and others have stressed its importance in temporal lobe epilepsy. If the child has obvious signs of cerebral damage the birth is blamed, but there is no obvious connection between labor and epilepsy occurring as a single manifestation much later. It is often impossible to obtain information of this most important stage of a person's life, which is probably another reason for underestimating its importance. The mother's description of her first view of the child, of its alertness and capacity to suck, may provide clues to damage. This factor is stressed because it is a field for prevention of epilepsy.

Lesions acquired after birth—As a child grows, its brain may be subjected to other traumatic influences too numerous to mention. Almost any cerebral lesion may lead to epilepsy.

Sudden onset of severe convulsions, sometimes unilateral, may coincide with evidence of gross cerebral damage. If the child lives, gross mental impairment or hemiparesis may remain. Encephalitis and cortical thrombophlebitis have been blamed, but pathologic correlation is curiously lacking.

With advancing age, the likelihood increases that the cause is an acquired lesion, but epilepsy without demonstrable cause may begin at any time of life. One cause which is effective throughout life is head injury. It is often difficult to assess the significance of a blow to the head during early life, but the frequency with which a convulsion occurs immediately or soon after a minor head injury is suggestive of more than coincidental association—although such reasoning may be very fallacious. The more severe head injuries associated with traffic accidents, occupation and missiles make the young to middle-aged man the greatest sufferer from post-traumatic epilepsy. Statistics vary greatly, but it is clear that infected compound fractures produce epilepsy in the highest proportion of cases, whereas closed injuries of civilian life are far less effective in its production. Ascroft[18] found that the incidence of epilepsy in 129 cases of gunshot wound, without penetration of the dura, was 23 per cent, while Rowbotham[19] found epilepsy in 2.5 per cent of 430 blunt-type injuries of peacetime in which the patients were examined not less than five years later.

Subdural hematoma secondary to trauma produces epilepsy in 10 to 25 per cent of cases. Subdural hematoma is often caused by the falls of chronic drunkards, in whom alcohol and perhaps other falls have already produced cerebral atrophy. A direct toxic effect may precipitate epilepsy after excessive intake of alcohol, and the atrophy produced by prolonged excess may lead to chronic epilepsy.

Apart from alcohol, other toxic and metabolic factors must always be borne in mind. Hypoglycemia, a rare cause, may remain unsuspected.

Neoplasms may be responsible for some 30 per cent of the epilepsies of late onset. Slow-growing neoplasms, especially meningiomas and oligodendrogliomas, may produce epilepsy long before they produce other manifestations. The slower-growing tumors have a greater tendency to produce epilepsy than do those which grow rapidly; e.g., seizures occur as the initial symptoms in 70 per cent of astrocytomas and 60 to 65 per cent of meningiomas, in contrast to 40 to 50 per cent of glioblastomas. The epilepsy such neoplasms produce is often of localizing value although convulsions may apparently be generalized. The possibility of malignant metastases must be kept in mind, especially in elderly patients, although occa-

sionally the primary growth may evade being detected.

My experience of investigation of patients between the ages of 35 and 55 years does not bear out the commonly made statement that cerebral neoplasm is most likely to be the cause of epilepsy during these two decades of life. Hypoplasia or undetectable causes appear to be more common. Damage to the brain during gestation, at birth, in early life, even by illnesses which gave no definite evidence of cerebral involvement, trauma, and atrophic processes of unknown causation all have to be considered as etiologic factors in epilepsy in an adult. As age increases, atrophic processes play a larger and larger part, especially as the incidence of neoplasm begins to wane. In elderly patients, cerebral atrophy is undoubtedly the most common cause of epilepsy. Cerebral vascular disease may lead to epilepsy by producing ischemic atrophy, metabolic disorders, and phases of sudden localized anoxia and edema.

Investigation of the Epileptic Patient

The aim of investigation is to exclude or recognize a treatable cause.

A tremendous amount of time, energy and money is expended in the investigation of the epileptic patient. It has a salutary effect to consider how few patients would suffer if investigation were impractical. It should be our aim to investigate patients who are likely to gain, and to avoid investigating others. It is necessary to keep clearly in mind the reasons for investigating: to recognize the site and nature of a removable cause, and to evaluate the type of ictal and interictal electric discharge when this is not apparent clinically. The choice of patient and the performance of the tests in such a way as to obtain the fullest information are thus matters for the expert.

The various investigative procedures will be discussed in order of frequency of usage.

Electroencephalography—Gastaut[15] has claimed about 80 per cent success with this test, using all methods of investigation. Other workers estimate their successes less conservatively at nearly 100 per cent. However, the diagnosis of epilepsy, and even of the type, may be clear on clinical grounds, and in these cases the tracing is of very little assistance. Also, a normal tracing does not exclude epilepsy, and abnormal tracings occur in nonepileptic persons. Only specific types of paroxysmal abnormalities are truly diagnostic.

The test may give valuable information in unusual attacks, and by its use one may properly assign to the epileptic group bizarre phenomena that might otherwise be called hysterical faints and behavior problems. In children abnormal interictal records may warn of an unfavorable outlook. Recognition of the nature of brief minor attacks, so often wrongly lumped together as petit mal, may indicate the need for drugs other than TRIDIONE®.

The electroencephalograph may localize focal discharges. By careful methods evidence of an origin in the temporal lobe may be found in a high percentage of cases, whether the cause is atrophic or neoplastic. When surgical removal of such foci, and of traumatic scars elsewhere, is being contemplated, the machine is an essential operative tool. In adults focal abnormality may warn of the presence of a neoplastic cause, and thus normality or abnormality is sometimes used as a guide to the need for further investigation. A normal tracing does not exclude neoplastic disease, and focal abnormalities are commonly found in patients in whom neoplasm cannot otherwise be demonstrated, although the passage of time may sometimes prove its presence.

Abnormality in a patient stabilized by treatment may be taken as an indication for continuing for a longer period.

Radiography of the skull—Like electroencephalograms, radiograms of the skull cause no inconvenience to the patient, other than a monetary one, but abnormality is much less common. However, abnormalities seen may be diagnostic of the presence and nature of many organic causes of epilepsy ranging from fractures and localized bulging due to hematomas or cysts beginning in early life to intracerebral calcification in toxoplasmosis, cysticercosis, aneurysms and tumors.

Pneumoencephalography—The chief use of this investigation is in the epilepsies of late onset.[20] Although evidence of neoplasm is ab-

sent, such a cause exists in something approaching 30 per cent. Pneumoencephalography is used in attempts at early diagnosis of neoplasm. It may fail in this regard, since minor asymmetries in the ventricular system may be developmental, or due to atrophy, and because a tumor may fail to produce recognizable abnormality until a late stage in its growth.

Angiography—This investigation has the unique property of revealing abnormalities of the blood vessels, displacements and pathologic circulations indicating the site and nature of neoplasms, angiomas and aneurysms. Curiously in problems of early diagnosis it is usually less informative than pneumoencephalography. When the intracranial pressure is raised, I favor ventriculography and angiography, but in such cases the problem is a neoplastic one, although epilepsy may have been one of the symptoms.

Lumbar puncture—Although a common investigation, lumbar puncture is rarely of value in diagnosis of epilepsy. Raised pressure, increased cellular content, raised protein, abnormal colloidal gold and a positive Wassermann reaction all give evidence of an organic lesion, but in a large number of epileptic patients no abnormality is found. Unless there is some reason other than the presence of generalized epilepsy, the test is usually of little potential value. It may be done prior to pneumoencephalography if one wishes to avoid the latter procedure in the presence of a raised pressure of which no other evidence exists. The fluid will always be examined when it is withdrawn at pneumoencephalography.

Since investigation of every case is hardly practical, a number of neoplasms will escape early detection, but careful clinical assessment and proper use of the more simple methods will reduce this number.

Treatment

Questions of surgical treatment depend on the presence of a removable cause. The need for operation in many cases of neoplasms which cause epilepsy is obvious. Removal of foci caused by trauma has not been universally carried out, and it is commonly accepted that operation should not be contemplated unless fits are frequent and medical treatment has failed. It would appear that excisions serve a valuable purpose when the attacks arise from the anterior end of the temporal lobe. However, choice of suitable cases is difficult and assessment over a number of years in surgical centers equipped to deal with such patients will be necessary before the operation gains wider usage.

Medical treatment has improved but the results are far from perfect. Most statistics suggest that it abolishes attacks in roughly one-third of cases, and in a number of these the attacks do not recur when treatment is stopped. In one-third the number of attacks is reduced, and in one-third treatment is ineffective. The number of cures is greatest when treatment is patiently careful, and in such hands the incidence of relief of attacks may considerably exceed this figure.[21]

Bromides, which commenced the modern era of medical treatment and were used for so long in treatment of grand mal, are rarely used nowadays. Sometimes they are useful as an addition to other forms of treatment.

For conciseness, the various other forms of medication, adult dosage and toxic effects are summarized in table 2. The dosage for children is, of course, less than that for adults.

Other attempts to alter biochemical conditions, e.g., ketogenic diets, have not been sufficiently helpful to stand the test of time. However, Tower[22] has found that the amino acids asparagine and choline are deficient in the epileptic brain, and treatment with these tends to return the biochemical state toward normal. Although the results of trials have not yet been recorded, it seems reasonable to hope that advances may result from biochemical measures, including those designed to alter the ionic concentrations at the cell membranes.

Status epilepticus—Repeated fits continuing without intervening recovery of consciousness constitute an epileptic emergency that may lead to death. One must watch the stage of hydration and nutrition and take care that the patient does not inhale saliva and mucus. Paraldehyde may be given in large doses by intragastric drip, intramuscularly (8 to 10

TABLE 2

MEDICAL TREATMENT OF EPILEPSY, DOSAGE AND TOXIC EFFECTS

DRUG	USES	DOSAGE	TOXIC EFFECTS
Barbiturates			
Phenobarbital	All forms of epilepsy	0.03 gm. to 0.06 gm. twice or thrice daily; 0.03 gm. in morning and 0.06 gm. at night is reasonable dosage	Drowsiness and lack of energy are most common ill effects, usually diminishing if dosage is continued. Irritability and overactivity not uncommon in children
N-methylethylphenyl-barbituric acid (prominal, MEBARAL®)	All forms. Less sedative but also less effective than phenobarbital	0.1 gm. twice or thrice daily	Safest and least upsetting of all forms of therapy
Hydantoinates			
Diphenylhydantoin sodium (DILANTIN®, EPANUTIN®)	Major and focal attacks. Useful in other forms of attacks except petit mal (said to be increased, although this is infrequent)	0.1 gm. three times daily, increased to six or seven times per day if necessary, or short of producing toxic symptoms	Swelling of gums is most common toxic symptom (dental attention before treatment and, if necessary, excision of gums), ataxia of gait and speech, nystagmus. Taking drug after meals may minimize digestive upsets. Transient morbilliform rash, and, rarely, a serious skin lesion which demands immediate withdrawal of drug
Methylphenylethyl hydantoin (MESANTOIN®)	As above. Used if Dilantin fails. It is metabolized to a toxic substance (NERVANOL®) which is no longer used for treatment because of toxicity. Should therefore be used with care	0.1 gm. thrice daily	As well as minor manifestations, severe hematologic complications and, rarely, erythema bullosum may occur
Oxazolidines			
Trimethadione (Tridione)	Petit mal. Said to increase grand mal, but this is not frequent	0.3 gm. three to six or even eight times a day	"Glare" phenomenon most common; going into sunlight produces dazzling monochromatic effect, like snowstorm. Effect may diminish with time; if not, change to other oxazolidines. Blood dyscrasias rare but dangerous, especially with higher doses. Regular blood counts advised, but may not detect effect until too late. Watch for fever, sore throat, etc. Rash and nephrosis also occur
3-Allyl-5-methyl-oxazolidine-2:4-dione (malidone)	Petit mal. Useful when Tridione fails or produces uncomfortable "glare"	Same as Tridione	Avoid if there is renal or hepatic damage. Blood dyscrasias less common than with Tridione. No "glare" phenomenon
3,5-Dimethyl-5-ethyloxazolidine-2,4-dione (PARADIONE®)	Same as above	Same as Tridione	Hematologic and renal complications less common than with Tridione; occasionally tinnitus

TABLE 2 *(continued)*

MEDICAL TREATMENT OF EPILEPSY, DOSAGE AND TOXIC EFFECTS

DRUG	USES	DOSAGE	TOXIC EFFECTS
Pyrimidines			
5-Phenyl-5-ethyl hexahydroprimidine-4:6-dione (MYSOLINE®)	Major and focal attacks, alone or in combination with Dilantin, if Dilantin fails. Other forms of epilepsy, except petit mal	0.25 gm. three to eight times per day	Nausea, vomiting and dizziness common after first dose, may subside. Transient drowsiness. Morbilliform rash may appear but is said to subside even if drug is continued. No gingival hypertrophy
LESS COMMONLY USED DRUGS			
Succinimides			
N-methyl-A-phenyl-succinimide (MILONTIN®)	Petit mal, some effect on grand mal	0.5 gm. three to eight times per day	Nausea, dizziness and drowsiness in small number. Transitory rashes and renal damage very rare
Acetylureas			
Phenacetylurea (PHENURONE®)	"Psychomotor epilepsy" only when all other forms of therapy have failed	0.5 gm. three to six times per day	Most toxic of all forms. Psychiatric symptoms common (20 per cent). Irritability. Liver disease. Aplastic anemia
Acetazolamide (DIAMOX®)	Petit mal	0.25 gm. three times daily	Drowsiness, gastrointestinal upsets

ml.) or intravenously (2 to 3 ml.). Intramuscular injections are painful, absorption may be poor, and an abscess may follow. Sodium phenobarbital (0.3 gm.) may be given intramuscularly or, preferably, intravenously and repeated in 30 minutes if attacks continue, with further doses and intravenous glucose if necessary. Intravenous anesthetics may be employed. The inhalation of chloroform formerly was standard treatment for prolonged convulsions in children; however, this may add other problems.

General rules—A number of general rules are insufficiently followed in treatment of epilepsy. If attacks are not suppressed, the dosage of the drug under trial must be increased to the limit of tolerance, and if necessary other drugs and combinations of drugs tried in sufficient dosage. Make changes slowly and do not lower dosage abruptly. Never be content when attacks remain.

If major attacks are happily controlled, continue with medication for three to four years, and only then gradually decrease the dosage, being prepared to restart if attacks recur. In petit mal it is reasonable to attempt reduction after one to two years.

Nonmedicinal measures—Interfere with normal life as little as possible. In general, only the driving of motor vehicles need be prohibited, for it involves danger to others. It may be reasonable to curtail swimming and horseback riding if this does not entail too much sacrifice. A farmer who depends on tractor driving for his livelihood may be allowed to decide for himself what measures he may take after the risks have been explained to him. The frequency and timing of attacks and the response to treatment are obviously important in such considerations. Some occupations which involve danger may need changing, especially if attacks are frequent. A child should not be taken out of school.

Every effort should be made to lead the patient (and parents) to believe that he is normal except for brief periods at the time of

the attacks. The old wives' tales of epilepsy, the lay dread of the disease, including fear of insanity, handed down as folklore, must be explained away. Fear of drugs is common and is to be counteracted by explanation. Psychologic abnormalities are countered by discussion, a point which has an importance out of all proportion to the brevity of this sentence. Questions are often asked regarding marriage, hereditary factors and having children. The physician has no right to prevent marriage, but he should urge that the partner is told of the attacks. There is nothing more shattering or, when previous attacks have occurred, more productive of future mistrust than an unexpected epileptic attack witnessed by night after marriage. If the person to whom the patient is engaged knows beforehand, human nature usually responds well to the situation and often a protective instinct is aroused. The risk of having epileptic children can be discussed statistically. In general it may be said that the risk is somewhat higher than in other families and considerably higher if both parties are epileptic. It is of interest that the incidence of epilepsy has not been lowered in Sweden where the marriage of epileptic persons is illegal.

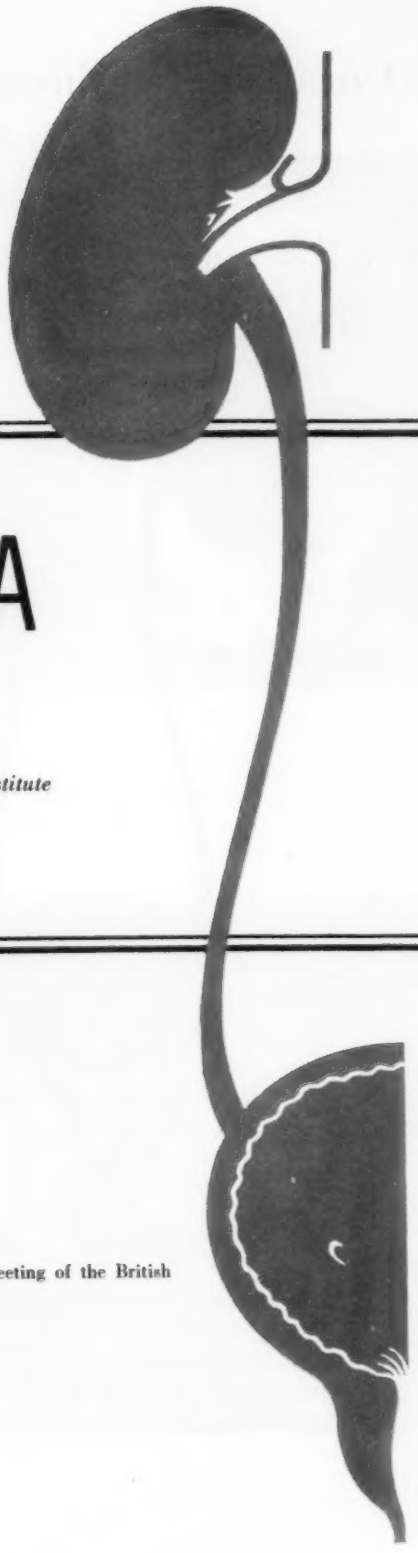
REFERENCES

1. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases. London, J. & A. Churchill, 1901.
2. ——: A Manual of Diseases of the Nervous System. Ed. 2. London, J. & A. Churchill, 1893.
3. Gibbs, F. A., Gibbs, E. L. and Lennox, W. G.: Cerebral dysrhythmias of epilepsy: Measures for their control. Arch. Neurol. & Psychiat. 39:298, 1938.
4. Gibbs, F. A. and Gibbs, E. L.: Atlas of Electroencephalography. Boston, Massachusetts, Lew A. Cummings Company, 1941.
5. Gibbs, E. L., Fleming, M. M. and Gibbs, F. A.: Diagnosis and prognosis of hypsarhythmia and infantile spasms. Pediatrics 13:66, 1954.
6. Gibbs, F. A.: Changes in generalized and focal seizures with age. Proceedings of the Fourth Congres International d'Electroencephalographie et de Neurophysiologie Clinique. Acta med. belg., p. 9, 1957.
7. Wilkins, L.: Epilepsy in childhood. J. Pediat. 10:317-357, 1937.
8. Budge, E. M.: Epilepsy and Convulsive Disorders in Children. New York, McGraw-Hill Book Co., Inc., 1949.
9. Lennox, M. A.: Febrile convulsions in childhood. Epilepsy. A. Res. Nerv. & Ment. Dis. Proc. 26:343, 1947.
10. Carey, W.: Febrile convulsions in infancy and childhood. M. J. Australia 2:254, 1956.
11. Bickford, R. G.: Electroencephalographic and clinical responses to light stimulation in normal subjects. (Abstract.) Electroencephalog. & Clin. Neurophysiol. 1:126, 1949.

11a. Bickford, R. G., Daly, D. and Keith, H. M.: Convulsive effects of light stimulation in children. Am. J. Dis. Child. 86:170, 1953; *see also* Robertson, E. G.: Photogenic epilepsy: Self-precipitated attacks. Brain 77:232, 1954.

12. Droogleever-Fortuyn, J.: On the pathophysiology of petit mal. Proceedings of the Fourth Congres International d'Electroencephalographie et de Neurophysiologie Clinique. Acta med. belg., p. 259, 1957.
13. Jasper, H. H. and Droogleever-Fortuyn, J.: Experimental studies on the functional anatomy of petit mal and epilepsy. A. Res. Nerv. & Ment. Dis. Proc. 26:272, 1947.
14. Penfield, W. G. and Jasper, H.: Highest level seizures. A. Res. Nerv. & Ment. Dis. Proc. 26:252, 1947.
15. Gastaut, H.: The Epilepsies. Springfield, Illinois, Charles C Thomas, 1954.
16. Ingalls, T. H.: Causes and prevention of developmental defects. J.A.M.A. 161:1047, 1956.
17. Courville, C. B.: Contributions to the study of cerebral anoxia. Bull. Los Angeles Neurol. Soc. 15:99, 1938.
18. Ascroft, P. B.: Traumatic epilepsy after gunshot wounds of the head. Brit. M. J. 1:739, 1941.
19. Rowbotham, G. F.: Acute Injuries of the Head. Edinburgh, E. & S. Livingstone, 1942.
20. Robertson, E. G.: Pneumoencephalography. Springfield, Illinois, Charles C Thomas, 1957.
21. Forster, F. M.: Modern Therapy in Neurology. London, Henry Kimpton, 1957.
22. Tower, D. B.: Mechanisms of seizures investigated by experimental production and control of a biochemical lesion present in epileptogenic cortex. Epilepsia, Series 3, p. 88, 1952.

SCIENTIFIC EXHIBIT



HEMATURIA

ALLAN CLAIN

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Royal Marsden Hospital and Institute
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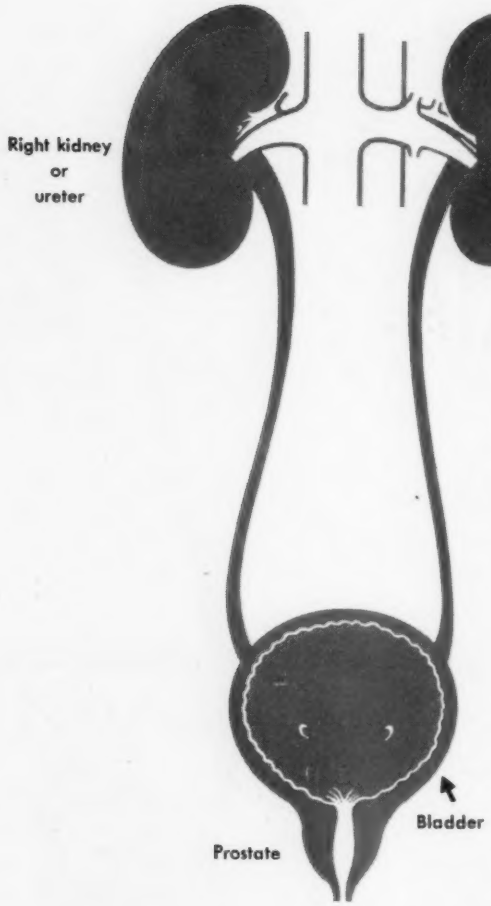
Adapted from an exhibit presented at the 1957 annual meeting of the British Medical Association.

Hematuria Is an Emergency

and if bleeding continues justifies an immediate cystoscopy to determine if blood is coming from:



Causes of Hematuria	Per Cent
Tumor	56
Prostate	19
Stones	7
Infection	6
Tubercle	3

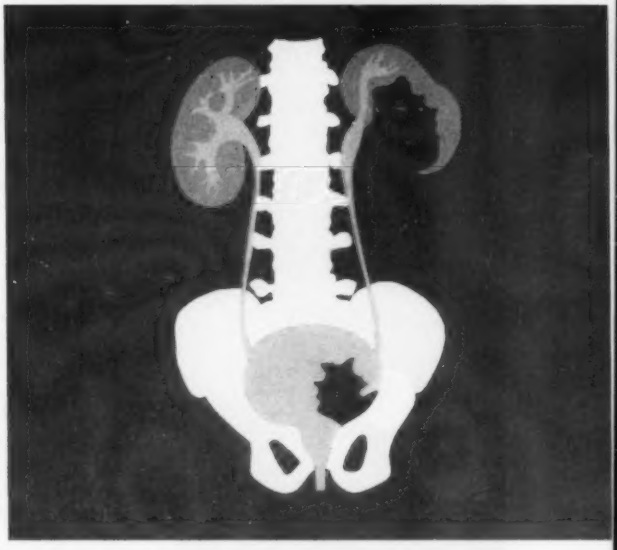
It is not enough to find a lesion which could cause hematuria. The remainder of the renal tract must be proved clear of any other lesion or disease. Multiple conditions can exist at the same time. These may include:

Malignant hypertension
Tubercle
Hydronephrosis
Polycystic disease of kidneys
Ureteral stones
Bladder stones
Diverticulum of bladder
Sepsis
Enlarged prostate
Carcinoma of prostate
Solid tumor of bladder
Papillary tumor of bladder
Tumor of ureter
Papillary tumor of renal pelvis
Adenocarcinoma of kidney

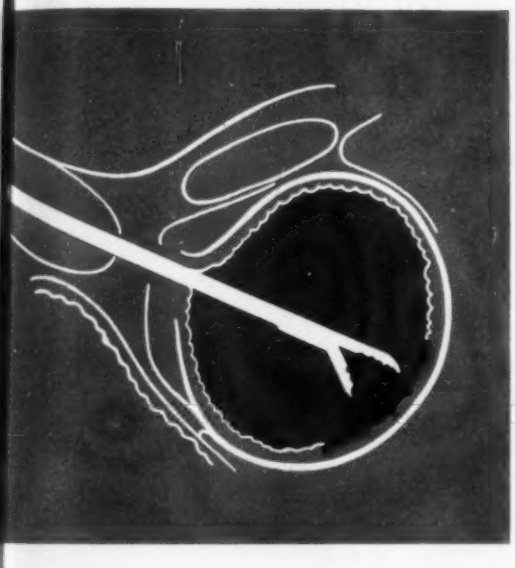
If bleeding has cleared up:

1. Culture the urine before giving any chemotherapy.
2. Take blood pressure.
3. Do intravenous pyelogram.
4. Do cystoscopy.

At Elective Cystoscopy...



A retrograde pyelogram may be required if a doubtful lesion is found on intravenous pyelogram, even if there is a lesion in the bladder.



Biopsy of a tumor or doubtful tumor may be required.

A bimanual examination under full anesthesia may be necessary to determine presence or absence of infiltration.

Mistakes in Diagnosis

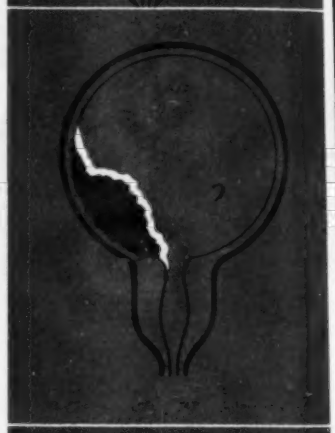
◀ Mucosal carcinosis may be misdiagnosed as cystitis. A sterile urine with pus means tubercle or tumor.

Hypernephroma may occur with enlarged prostate. Do intravenous pyelogram in all cases. ▶

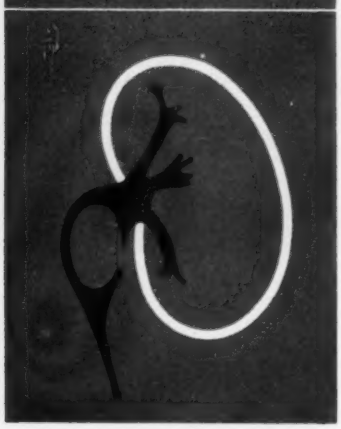
◀ Stones and tumor may coexist. Do biopsy on doubtful lesions.

Papillary tumor of renal pelvis may precede or follow papillary tumor of bladder. Do intravenous pyelogram in all cases. ▶

◀ Anaplastic tumors may appear small cystoscopically but may have invaded widely. Do bimanual examination on all cases. Do biopsy on bladder tumor(?)



Slough or phosphatic deposits may overlie tumor. ▶



◀ A filling defect may be a blood clot. Repeat intravenous or retrograde pyelogram if there is recent history of bleeding.

The bladder may be invaded by carcinoma of adjoining organs. ▶

Australia's rapid growth and expansion have emphasized the medicosocial problems involving increasing numbers of aged and permanently disabled persons. Until recently the medical profession had not acknowledged the role that associated professional disciplines and paramedical services must play in developing rehabilitation programs. Physical medicine and occupational and physical therapy departments in hospitals are still in the embryonic stage. Effective rehabilitation programs can be established only through the leadership of the medical professions and the cooperation of voluntary and governmental services.

Rehabilitation in Australia

ITS INTEGRATION IN MEDICAL SERVICES AND MEDICAL INSTRUCTION

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THROUGHOUT the world, during the past decade or so, the word "rehabilitation" in relation to medical practice has indicated a new approach to the complete care of all disabled persons in a modern community with all its inherent demands. It is a word which has become commonplace, yet through glib use is tending to lose its true significance for many of us.

In describing rehabilitation programs that have been developed in Australia to the present time, and the medical profession's participation, it is hoped to underline some general aspects of the matter which, it is believed, are of universal interest and worthy of consideration or reconsideration by all physicians.

It is generally true that the problems of disabled persons are largely influenced by the community in which they live. The attitude of the public, and of special sections of it, based on education, knowledge and traditions, can greatly affect the assistance and the services offered to the disabled. The plight of the disabled is more recognizable in densely populated and highly industrialized communities, and becomes more urgent when these communities are affected by industrial depression or recession. In times of war the need for rehabilitation or total care is universally recognized because of the greater incidence generally of disability and of manpower shortages.

How does this apply in Australia?

Australia is a relatively young country, having been first settled in 1788. It has suffered two local economic depressions in the early

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and late nineteenth century, and the world-wide depression of the early 30s of the present century. The two world wars have also made great demands on its economy, its primary and industrial resources, and its manpower. While Australian economy has relied traditionally on constantly increasing primary production, there has been a marked movement toward industrial self-sufficiency in the last 12 years.

This development has taken place in a continent of three million square miles with a population of 10 million people, 54 per cent of whom live in the capital cities of the six states, another 25 per cent in the provincial city areas, and 20 per cent in rural areas. Since the turn of the century the proportion of persons over the age of 65 years has increased from 4 per cent to 8.3 per cent, and although there has been a fairly long-term decline in the proportion of children, recently, due to the higher rates of natural increase and to large numbers of young people among migrants from Britain and Europe, this decline has been reversed.[1]

It is also important to note that, due to natural increases and to the intensive immigration policy, this Australian population has grown at the rate of 2.5 per cent per year over the past 10 years, which makes Australia one of the most rapidly expanding countries in the world today. This growth in population and this industrial development and expansion have naturally introduced new problems and emphasized others that have existed, partially unrecognized, for many years. Not the least of these are medicosocial in nature, for example, the ability of increasing numbers of disabled persons to work and exist, along with the able, in a highly competitive industrial setting, and the problem of increasing numbers of aged persons. These are two clear challenges to Australian medicine.

By and large, however, the medicosocial problems created in a comparatively uninformed and therefore unresponsive public through increasing numbers of aged and permanently disabled persons have not, until very recent times, been fully appreciated by the local profession as a whole. Only in the last five years has the profession displayed evidence of assuming its fundamental responsibility to lead in the solution of these matters. More specifically is this true in relation to the aged and to disabled persons in the young adult and middle-aged groups. The disabled child or adolescent, on the other hand, has long had the interest and concern not only of the medical profession but of voluntary social welfare agencies and of the public in general.

On the whole, the needs of the infirm aged are regarded at the moment as deserving of more urgent attention by all professional groups, and are more readily understood by the general community than are the needs of disabled persons in the age groups of young adulthood and middle age. This is probably so in other countries, but it tends to indicate, so far as treatment services are concerned, a fundamental fault or deficiency in the approach to the problem of disability.

Generally it is true that, allowing for the special problems of different age groups, there is a common basis for the proper treatment of physical, psychologic, social and economic problems of disabled persons in all age groups; and it is medicine's responsibility to establish and ensure this.

Largely because medicine has been slow in acknowledging its fundamental responsibility, rehabilitation services which exist in Australia meet the needs of special groups only, not of all disabled persons who require them. Some of these services have been developed to meet the total needs of disabled persons, while others are incomplete. They have been developed, too, at different times by voluntary and governmental organizations; and while each may function as a separate and autonomous service, and while there is a recognizable need for their coordination, to date no plan for this coordination has been prepared.

It is interesting to note the history and development of these several services.

Voluntary Organizations

Apart from early efforts by voluntary organizations to provide facilities for education and vocational rehabilitation of the deaf and

blind, the first general group of persons with locomotor disability to capture the attention and interest of the public in Australia were the children. From 1929, when the New South Wales Society for Crippled Children was formally established, there was a progressive development of similar organizations in the other states. These voluntary bodies owe their origins to the sympathy and interest of groups such as Rotary, the generosity of the public as a whole, and of individual philanthropists in particular.

In their work the societies have received the guidance, advice and service, in an honorary capacity, of individual members of the profession in planning and case work. Generally the societies have done very commendable work in meeting certain important needs of disabled children, especially in maintaining registers of handicapped children and providing, with some degree of coordination, home care, club activities and education. In New South Wales the society established its own hospital service prior to 1939, but it is of interest that although the various state societies have been functioning for 20 to 30 years the New South Wales Society is the only group to have appointed a full-time medical director or superintendent—and that as recently as 1956.

Until 10 years ago, no coordinated facilities existed in Australia to meet the special needs of cerebral palsied children. During the past decade, through the efforts of parents and friends, individual state societies or associations for the welfare of spastic children have developed. These associations have established "spastic centers," the first being in Sydney some 10 years ago. From their inception these centers have generally been organized under experienced and inspired medical direction and on the whole are excellent examples of rehabilitation services which meet all the needs of a special group of children. This is especially true of the center in Sydney, which represents one of the best of its kind in the world.

In the last 10 years, also, other organizations have been established as the result of the interest and efforts of relatives and friends of handicapped persons, mostly in older age groups. Thus have been established the Association for the Civilian Maimed and Limbless, the Poliomyelitis Society of New South Wales, the Paraplegics Association of Australia, the Multiple Sclerosis Society of Australia, The Association for Mentally Retarded Children, and so on. The Association for the Civilian Maimed and Limbless has been very active in the field of sheltered employment, and in New South Wales has done outstanding work in setting up a cooperative workshop.

While the remaining groups have developed only minimal, if any, facilities for the care of those disabled persons they represent, they have undoubtedly brought to public notice the plight in society of the more adult disabled and have helped considerably in getting the attention of professional groups and of governments. They have been specially able to effect this through a federal organization which represents all such voluntary organizations in Australia, namely, the Australian Advisory Council for the Physically Handicapped. This council fosters the work of most of the voluntary agencies by means of a program of special and general education. It is the acknowledged national representative body in Australia of the International Society for the Welfare of Cripples.[2]

Governmental Services

Governments in Australia, at different times, have also assumed responsibilities that have direct or indirect effects on disabled persons. As in the United States, government in Australia is performed by federal and state legislatures. The federal government, through its Social Services Act, grants "invalid pensions" to permanently disabled persons from the age of 16 to 65 years, subject to special conditions. The first pensions were paid in 1910. Much more recently it has been enabled to grant "sickness benefits" to temporarily disabled persons, subject again to special conditions. These pensions and benefits are paid through the Commonwealth Department of Social Services.[3]

Since 1948, this department has also administered a rehabilitation service known as the Commonwealth Rehabilitation Service. Originally provided for recipients of invalid

pensions and unemployment and sickness benefits, the service has been extended to recipients of tuberculosis allowances, to disabled adolescents in the prepension age group, that is, 14 to 15 years, to insurance cases, and to privately referred patients on a repayment-for-service basis.

The Commonwealth Rehabilitation Service has established special facilities for evaluation and treatment in all states except one. Rehabilitation centers have been planned and staffed in accordance with accepted rehabilitation procedure, and provide a total program for all phases of rehabilitation that follow definitive surgical and medical care in hospitals. In case work the closest liaison is maintained with the private practitioner, diagnostic and treatment services in hospitals, social welfare agencies, statutory agencies, and employer and employee groups.[4]

The Service undoubtedly has a good record, having returned to economic security (as of May 1958) 10,300 persons who would have continued to depend on pensions for existence. This record reflects the ability and dedication of its staff, and the Service is respected by all who have been associated with it in its case work. It is not, however, a full community service, since it meets only the needs of a group which, although important, is nevertheless relatively small. Within this group it is further restricted since one of the conditions of eligibility is that there must be a reasonable prospect for an accepted patient taking up full-time normal employment after a specified period.

It is also an autonomous service which, while cooperating as fully as possible with medical and other agencies in the communities, is nevertheless administered and functions separately from the hospital and other essential services.

Other federal departments providing services for the disabled are the Repatriation Department, which, since the first world war, has cared for all problems (including medical care and pensions) of war-disabled veterans; and the Commonwealth Employment Service of the Department of Labour and National Service, which maintains a special section for placement of the disabled and works closely with the Commonwealth Rehabilitation Service and the hospitals in this important matter.

From the point of view of constitutional responsibilities, state governments in Australia have wider opportunities than the federal government for helping to solve in a more complete and fundamental way the community problem of disability. These opportunities, in the main, result from their direct responsibility, through health or hospital departments, for the coordination and administration of hospital services, including the financing of hospital construction and the addition of new services such as rehabilitation departments.

In the two larger states, New South Wales and Victoria, hospital services are coordinated by hospital commissions set up by the state governments, and these commissions assume responsibility for hospital construction and associated capital expenditure.

Little interest has so far been shown by these various state government agencies in enabling hospitals to develop facilities for rehabilitation.

It is apposite to note in passing that at present in Australia income tax is levied only by the federal government, which annually grants money to the states for their work, leaving them to decide how these grants are used. To such moneys states can add revenue obtained from local indirect taxation and, in two or three states, from "state lotteries," profits of which are largely used for the construction of hospitals.

The federal government, through federal-state agreements, makes direct capital grants to state public hospitals to establish adequate services for pulmonary tuberculosis; and, more recently, to state mental hospitals to help fight the increasing problem of mental disability. In addition, through its Hospital Benefits program, the federal government directly assists hospital maintenance by means of bed-per-diem subsidy of up to 12/- (about $1.30).

Despite the over-all coordination by and dependency for capital finances on state government agencies, each hospital is largely autonomous and functions under a hospital board of lay and medical members, to whom the hos-

pital's medical superintendent and chief executive officer is directly responsible. Specialist and consultant staffs of these hospitals are generally based on the honorary system, as in Britain prior to its National Health Service.

Role of the Medical Profession

There are at present five university medical schools established within the six states of the Commonwealth, and these schools are associated with approximately 18 teaching hospitals for instruction in clinical sciences. In addition there is a school of medical research at the National Post-Graduate University in Canberra.

The first medical school was formally established in Melbourne, Victoria, in 1862,[5] and since then Australian medicine has generally kept abreast of new developments and technics of treatment. While the demand on the available undergraduate teaching resources is pressing, the standard of training remains high and uniform throughout Australia. Postgraduate training of Australian physicians, abroad and at home, is very active, and has been greatly facilitated by the establishment of postgraduate medical committees in most of the state universities.

The practice of medicine in its various branches generally is of a high standard, and naturally, as elsewhere, has tended to become highly specialized. Despite this, very little has been done within hospitals to coordinate services to meet the complete rehabilitation needs of patients. Services which do exist for this purpose function largely in isolation and under no specific medical direction. This, of course, has an important bearing on the teaching of the philosophy and procedures of rehabilitation, as they should apply in a hospital setting, to medical and paramedical undergraduates.

How this should be done had been demonstrated within the medical services of the Australian armed forces during World War II, when fairly comprehensive medical rehabilitation programs had been organized. But, as in most countries, the practice of medicine in Australia since the war has continued, in general, along traditional lines. I believe it is true that here, as elsewhere, the majority of medical practitioners do not yet recognize that a physician alone cannot treat completely those of his patients presenting severe disability, unless he uses fully the skilled advice and assistance of others trained in allied medical and nonmedical fields.

It has always been acknowledged that teamwork, involving the closest cooperation among medical colleagues of different specialties, is desirable and often essential in defining diagnosis and treating the more urgent phases of illness. Yet the essential need for such cooperation, involving even a wider range of professional disciplines in the so-called third phase of medicine,[6] is not as fully appreciated.

In the acute hospital situation the doctor must be virtually the dictator of his team; but in this third phase he must deal with "a wider range of professional workers, some of whom do not have a tradition of subservience to the dictator in the hospital. To succeed, the physician must become a recognised leader rather than an obvious dictator."[7] He must also be able to secure and coordinate the services of associated professions, be prepared to seek opinions, and be able to discuss the treatment of a patient with professional persons not trained in medicine. Generally physicians find it difficult to consult these persons and place value on their suggestions.[8] Often this is because they do not fully appreciate the contribution these other professional disciplines can make to complete treatment.

This, I believe, is the fundamental reason impeding the development of rehabilitation programs in the large majority of Australian hospitals, more especially the teaching hospitals. It is also, I believe, the reason why paramedical professions have not developed more rapidly, are not used more extensively, or, where established within hospital services, are not fully integrated to meet the total needs of patients.

Paramedical Services

The paramedical professions have developed sporadically over the years and generally without relation to each other. Physical therapy is the most senior and readily accepted of these professions in Australia, having been

formally established in 1905 in Sydney, New South Wales. It is now a university diploma course in five states, and teaching hospitals actively participate in this training. In most hospitals it is usually found attached to the orthopedic department, under the direction and supervision of orthopedic surgeons.

Occupational therapy is much more junior and less recognized, the first school having been established in Sydney, New South Wales, during World War II, principally to meet the needs of the rehabilitation services of the armed forces. There are now three schools in all affiliated to teaching hospitals. Occupational therapy is still largely not understood by Australian physicians, nor is it used in all hospitals. Most teaching hospitals now have occupational therapists on their staffs, but it is rare to find an occupational therapy department fully developed and providing a full range of technics that are essential for complete rehabilitation.

Speech therapy services are generally found in pediatric hospitals and medical agencies, where they meet an obvious need, but speech therapy still is not as extensively used in general hospitals for adults and for aged persons.

The training of medical social workers, or, as they are known in Australia, hospital almoners, dates from 1930. Social studies is now an established course at four universities and affiliated to teaching hospitals for almoner training. While the need for social workers in modern communities in Australia has been well established, recognition of their work generally and in a medical setting has been slow and greater numbers are needed in hospitals.

It is probably because physicians, both in private and in hospital practice, do not understand and support the contribution to patient care by all these paramedical groups that greater numbers are not encouraged to train in the various disciplines. It also explains why their integration in a hospital rehabilitation service under enlightened medical direction is not as yet a reality in most hospitals.

Physical Medicine as a Specialty

Physical medicine as a specialty has had a slow climb to recognition by other medical and surgical specialties but remains underestimated. Most of those who practice as consultants in physical medicine have received additional training and qualification overseas, there being no postgraduate course in Australia. There is, however, an Australian Association of Physical Medicine and Rehabilitation which, through regional and national medical congresses, is attempting to develop an interest and knowledge of rehabilitation among other special groups of the profession.

Some Australian hospitals have developed departments of physical medicine, in which occupational therapy and physical therapy are generally under the direction of the honorary consultant in physical medicine. These departments are, at the most, only embryonic rehabilitation departments.

Comment

This, then, is the general picture, but it would be wrong to conclude that the prospects are not hopeful. There is evidence now of an awakening interest in the profession, and there is a growing band of physicians who recognize what is needed, especially in the teaching hospitals and more generally in the community. Enlightened younger physicians associated with the staffs of teaching hospitals who have had opportunities for postgraduate study in some of the recognized medical programs abroad are pressing for similar programs in Australian hospitals. Some hospitals are making a beginning.

Recently the British Medical Association in Australia, regarding rehabilitation of the disabled as a national problem, resolved at a Federal Council meeting to petition the Commonwealth Government for financial aid to hospitals for the building of extra facilities for rehabilitation within hospitals, especially the teaching hospitals, quoting as precedent the Commonwealth-State program in the successful fight against tuberculosis.[9,10] No one knows at present what the result of this proposal will be.

Possibly in Australia some program similar to that administered in the United States by the Office of Vocational Rehabilitation of the Department of Health, Education, and

Welfare, under U. S. Public Law 113, may "boost" rehabilitation in Australia.

There can be little argument, however, that effective rehabilitation programs, both within and without hospitals, for all disabled persons of any age group depend on the able leadership of the medical profession.

Conclusion

I believe it can be said without great fear of contradiction, taking Australia as an example, that the fundamental impediments to good rehabilitation have been (1) the inability of physicians generally to acknowledge the vital contribution and joint responsibility in patient care of professional disciplines outside medicine itself, all of which, with medicine, should be regarded nowadays as "the greater medical profession"; (2) the inability of physicians within their own ranks, especially in a hospital setting, to agree who should be responsible for a rehabilitation service—which specialty should assume responsibility for the supervision or direction of rehabilitation; and consequently (3) the inability to recognize that a rehabilitation service in a hospital setting is a dynamic treatment and a consultative service.

Enlightened and inspired medical leadership, no matter what the specialty, will provide coordination of services for all from a common basis; will facilitate more efficient research into physical, social and economic problems of disability; will promote better training programs in rehabilitation methods and technics for undergraduates in medicine and the paramedical disciplines; will eventually result in the better understanding of disabled persons, and consequently better cooperation in their rehabilitation by the public at large, and more especially employer and employee groups, thus ensuring their economic independence.[11]

The views expressed in this paper are my own and do not necessarily reflect the views and policy of the Commonwealth Department of Social Services in Australia and of its Rehabilitation Service.

I wish to thank the Director-General, Commonwealth Department of Social Services, Australia, for his permission to publish this paper.

REFERENCES

1. Bulletin of the International Social Security Association (June) 1957.
2. Tuxen, J. (Secretary, Australian Advisory Council for the Physically Handicapped): Personal communication.
3. The Commonwealth of Australia, Social Services Act 1947/55.
4. The Commonwealth Rehabilitation Service (issued October 1957).
5. Russell, K. F. (University of Melbourne): Personal communication.
6. Rusk, H. A.: Rehabilitation: The third phase of medicine. Industrial Hygiene and Occupational Medicine, 1950.
7. Darling, R. C.: The future of physical medicine: The need for medical statesmanship. Am. J. Phys. Med. 36:193, 1957.
8. Worthingham, C.: The future of physical medicine: Relations to other professions concerned with rehabilitation. Am. J. Phys. Med. 36:325, 1957.
9. Australasian Medical Congress, Tenth Session: Meeting of Federal Council, British Medical Association. M. J. Australia 1:508, 1958.
10. Commonwealth of Australia, Tuberculosis Act of 1948.
11. Burniston, G. G.: Education of professional workers concerned with the care and welfare of the disabled. Proceedings of the Seventh World Congress, International Society for the Welfare of Cripples, London, 1957.

Success in treating lymphosarcoma of the tonsil depends on early diagnosis. The disease is characterized either by sudden and rapid unilateral enlargement of the tonsil or by a superficial ulcer which later becomes very deep and extensive. Early symptoms are negligible and should be confirmed by examination for Vincent's microorganisms and subsequent section and microscopic examination of the dissected tonsil. Recommended treatment is complete removal of the tonsil, followed by radiotherapy.

Lymphosarcoma of the Tonsil

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ALTHOUGH lymphosarcoma of the tonsil is a comparatively rare disease, success in treatment is bound up with early diagnosis, and unless the general practitioner recognizes early enough that the condition is a serious one and refers his patient at once to a laryngologist, any treatment will be in vain. I have personally seen only 12 cases of lymphosarcoma of the tonsil during my professional life, but it is possible that many cases are missed, for in the small community in which I now live (just under 25,000 population) I have encountered three cases in three years. It is not uncommon for a lymphosarcoma of the tonsil to be considered a tonsillar abscess (which, indeed, it may resemble) and attempts made to "open" it; and other (ulcerative) cases have been called Vincent's angina until bacteriologic examination has proved this diagnosis to be false.

Because of its comparative rarity, even experienced laryngologists have published opinions on the condition that are not at all in accordance with my own experience. E. D. D. Davis,[1] who opened a discussion on this subject at the Royal Society of Medicine in London in 1941, said that all the patients with lymphosarcoma whom he had seen "died within 18 months from the time that the first symptoms appeared." Gwen Hilton, H. A. Lucas and Joan Wadge[2] in 1953 said that lymphosarcoma of the tonsil "is usually discovered because of the accompanying upper cervical adenitis, which may be the only abnormality the patient notices." J. F. Simpson, I. G. Robin and J. C. Ballantyne[3] said in 1957 that "lymphosarcoma and reticulosarcoma occur in the tonsils and other lymphoid areas of the oropharynx in young adults and sometimes in children."

Most of my patients (though not all) have been more fortunate than those of E. D. D. Davis, doubtless because in most cases the condition was recognized early by their family

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FIGURE 1. Lymphosarcoma of the tonsil, type 1.

FIGURE 2. Lymphosarcoma of the tonsil, type 2.

doctors. I have indeed one patient, Miss R., whose lymphosarcoma of the left tonsil I removed by diathermy as long ago as July 1934, and I am informed that she is well and "debris was removed from her left ear at the Metropolitan Ear, Nose and Throat Hospital on 10th June, 1954." After removal of the tumor (the diagnosis was confirmed microscopically), she at once received a course of x-ray therapy by Dr. R. Moore Patterson of the National Temperance Hospital, London.

I have personally never seen a case of lymphosarcoma of the tonsil that was characterized first by cervical adenitis. And I have never yet seen a case in a child. Most of my cases have been in adults in their thirties and forties, and one patient was a man aged 73 years.

As regards its incidence, J. I. Munro Black[4] (1938) recorded seven cases, E. D. D. Davis[1] (1941) 14 cases, and V. E. Negus[5] (1941) "five or six cases." M. Lederman,[6] the radiotherapist, of the Royal Marsden (formerly Cancer) Hospital, London, tells me that from 1945 to 1956 they have had there 37 cases of sarcoma of the tonsil. R. A. Willis[7] (1953), the English pathologist, had 34 necropsy cases of lymphosarcoma (not only of the tonsil) and found it "predominantly a disease of middle and old age," though in his experience it was not rare in youth, even in infancy.

Pathology

There are two main types of lymphosarcoma of the tonsil (figures 1 and 2): (1) a sudden and rapid unilateral enlargement of the tonsil and (2) a type in which the tonsil is at first not noticeably much enlarged but there is a superficial ulcer which later becomes very deep and extensive. It is said (by E. D. D. Davis and others) that there is a third type, which shows a mass of enlarged cervical glands first and the primary growth becomes evident later. I have not come across this type. When I have found a mass of enlarged cervical glands, without other evident signs or symptoms, I have usually found the primary growth in the pyriform fossa.

The name "lymphoma" has been given to any growth of the lymphoid tissue and has been subdivided into malignant and benign lymphoma. The malignant lymphomas include lymphosarcoma, lymphadenoma, multiple

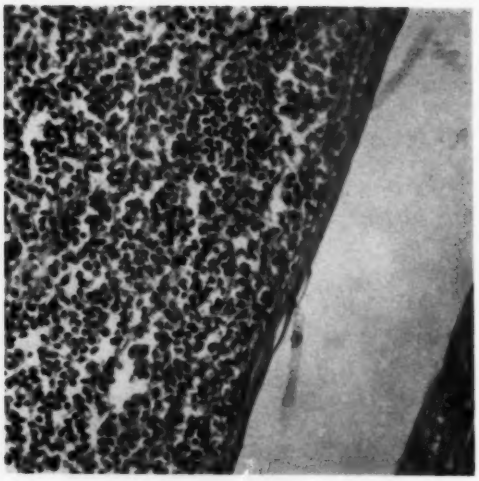

FIGURE 3. Lymphosarcoma of the tonsil, x 110.

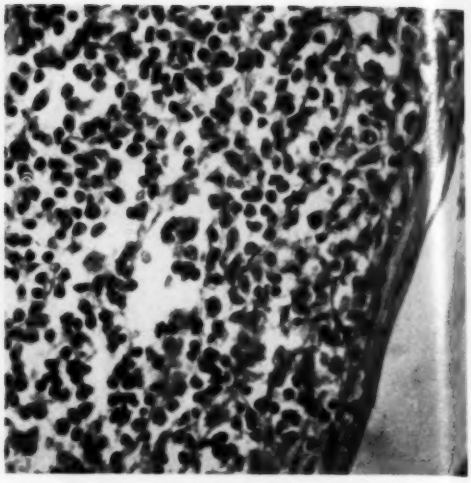

FIGURE 4. Lymphosarcoma of the tonsil, x 330.

myeloma and lymphatic leukemia. "Lymphosarcoma" means a malignant tumor of lymphoid tissue which is predominantly lymphocytic or lymphoblastic in structure. It includes both "lymphocytomas" and "lymphoblastomas," the distinction between which is entirely arbitrary and depends only on the degree of differentiation of the malignant lymphoid cells. Gall and Mallory[8] (1942) found leukemia in 48 per cent of cases of lymphocytoma and in 38 per cent of cases of lymphoblastoma.

R. A. Willis,[7] the pathologist, has stated (1953) that lymphosarcomas "characteristically consist of diffuse masses of rounded cells of uniform size closely resembling either mature lymphocytes or immature lymphoblasts and showing few or many mitotic figures according to their degree of anaplasia. . . . The cells penetrate into all the available interstices of the invaded tissues, mingling inextricably with the surviving components of these." (Figures 3 and 4.)

Diagnosis

Early diagnosis lies in the hands of the general practitioner, for the symptoms are usually so slight—some discomfort in the pharynx or some trifling interference with swallowing—that the patient is almost apologetic in consulting his doctor. But when the general practitioner, in making a routine examination of an adult, observes in the throat a marked unilateral enlargement of one tonsil, sometimes with an ulcer, he must not waste what may prove invaluable time in trying the effect of paints or gargles, but should refer the patient forthwith to a laryngologist.

The laryngologist may swab the ulcer, if present, and have it examined for Vincent's microorganisms; if this is negative he will be well advised to carry out biopsy of the suspected tonsil at once. I am personally very chary of punching out a piece of the tonsil (or any other part of the pharynx) for biopsy; as opposed to the larynx, where this is safe, in the pharynx it may help to spread the growth, though I know that some laryngologists do not share my qualms. I prefer to dissect out the complete tonsil, preferably (in a suspected lymphosarcoma) using diathermy when available (figure 5).

Section and microscopic examination will confirm (or otherwise) the diagnosis, though sections of the whole tonsil may have to be examined carefully before lymphosarcoma can be excluded.

Treatment

Lymphosarcoma is markedly radiosensitive, but it is not unknown for the primary growth

and any enlarged cervical glands to disappear rapidly after treatment, yet for secondary growths to appear within a year in the chest or abdomen. Two of my patients, who had radiotherapy only, were dead from recurrences within eight months. I had at that time been influenced by the writings of Berven[9] and other radiotherapists to look on this as the ideal method of treatment. But nowadays I should always first remove the tonsil carefully and completely, have it examined microscopically, and, if the diagnosis of lymphosarcoma is confirmed, at once send the patient for x-ray or radium therapy.

Here are notes of a recent case. Mrs. C., 40 years of age, was referred to me by her doctor because of a persistent ulceration of the right tonsil. She had, in fact, to persuade her doctor to allow her to consult a laryngologist. I first saw her on November 14, 1956. The condition looked like Vincent's angina, but when bacteriologic examination for this proved negative, on November 29 I dissected out the right tonsil (in the Military Hospital, Gibraltar) and had it examined by the pathologist, who pronounced the condition to be lymphosarcoma (see figures 2, 3 and 4). The patient was then sent to England for radiotherapy, treatment being begun by Dr. I. G. D. Bell, consultant in therapeutic radiology, Rochester, Kent, on December 11. Her pharynx and neck were irradiated by means of two opposing 10 by 8 cm. fields, using 250 kv x-rays at H.V.L. of 2.4 cu. mm. Applied dose was 3400 r, minimum tumor dose 3300 r, maximum skin dose 3700 r in 21 days. Bilateral earache developed, with resultant otitis media on the left side, which cleared very slowly. She became extremely hoarse with the reaction to treatment, but the voice gradually recovered completely. Dryness of the mouth and loss of taste persisted for a long time. When the patient was last seen, the pharynx was well healed, and there were no enlarged cervical glands and no untoward signs or symptoms.

Conclusion

I have become convinced that in lymphosarcoma complete removal of the affected tonsil, whether by dissection or by diathermy—which in any case is necessary for biopsy—is an essential preliminary to the further treatment by x-rays or radium.

FIGURE 5. Lymphosarcoma of the tonsil in a man aged 73 years, completely dissected out by diathermy.

REFERENCES

1. DAVIS, E. D. D.: Lymphosarcoma of the tonsil. J. Laryng. & Otol. 56:302, 1941.
2. HILTON, G., LUCAS, H. A. and WADGE, J.: Malignant disease of the pharynx. In WATKYN-THOMAS, F. W. (ED.): Diseases of the Throat, Nose and Ear. London, Lewis, 1953, p. 278.
3. SIMPSON, J. F., ROBIN, I. G. and BALLANTYNE, J. C.: Tumours of the oropharynx. In Synopsis of Otorhinolaryngology. Bristol, England, Wright, 1957, p. 237.
4. BLACK, J. I. M.: The lympho-epitheliomata. J. Laryng. & Otol. 53:225, 1938.
5. NEGUS, V. E.: Clinical aspect of lymphosarcoma of the tonsil. Proc. Roy. Soc. Med. 34:682, 1941.
6. LEDERMAN, M.: Personal communication, 1957.
7. WILLIS, R. A.: Pathology of Tumours. Ed. 2. London, Butterworth, 1953, p. 755.
8. GALL, E. A. and MALLORY, T. B.: Malignant lymphoma. Am. J. Path. 18:381, 1942.
9. BERVEN, E. G. E.: Malignant tumours of tonsils. In: PACK, G. T. and LIVINGSTONE, E. M. (ED.): Treatment of Cancer and Allied Diseases. New York, Paul B. Hoeber, Inc., 1940, p. 409.

Prevention of infection is of primary importance in management of compound fractures. At Queen Mary Veterans' Hospital, Montreal, debridement and application of split-skin grafts have yielded impressive results in such injuries. This procedure proved effective in the six cases presented by the authors. In three cases, there was gross contamination with extensive soft-tissue damage and skin loss; infection developed before therapy was instituted in the other three cases.

The Management of Infection in Fractures

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In July 1954 we[1] reported the results of treatment of a group of cases of chronic bone infection by immediate skin grafting of the debrided lesion, followed when necessary by filling-in of the defect with cancellous bone chips covered with a pedicle of skin and subcutaneous tissue. The method is divided into two stages, which are described briefly in the succeeding paragraphs.

First, all scarred, fibrotic and necrotic soft tissue is excised. The infected and sclerosed area of bone is then widely excised, leaving a surface of healthy bone which bleeds freely. Following this, the whole area is thoroughly irrigated with normal saline solution and a split-skin graft of suitable size is applied, covering both bare bone and denuded soft tissue. The graft is sutured to the margin of the wound, and coaptation in the surface is obtained by a meticulously applied pressure dressing. The part is then immobilized in plaster. The first dressing is done at about 10 days, and other dressings are applied as it becomes necessary.

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The second stage consists of excision of the split-skin graft, freshening of the bone surface by curettage, and filling-in of the defect in the bone, preferably by cancellous bone chips, or, when indicated, by cortical bone with cancellous bone chips packed about it. The surface is then covered with a pedicle graft of skin and subcutaneous tissue obtained from contiguous tissue or brought from another part of the body by a pedicle or a tube-pedicle graft. Figures 1 and 2 illustrate the two stages of the procedure.

We are continuing to use this method to treat chronic bone infections, and we find that

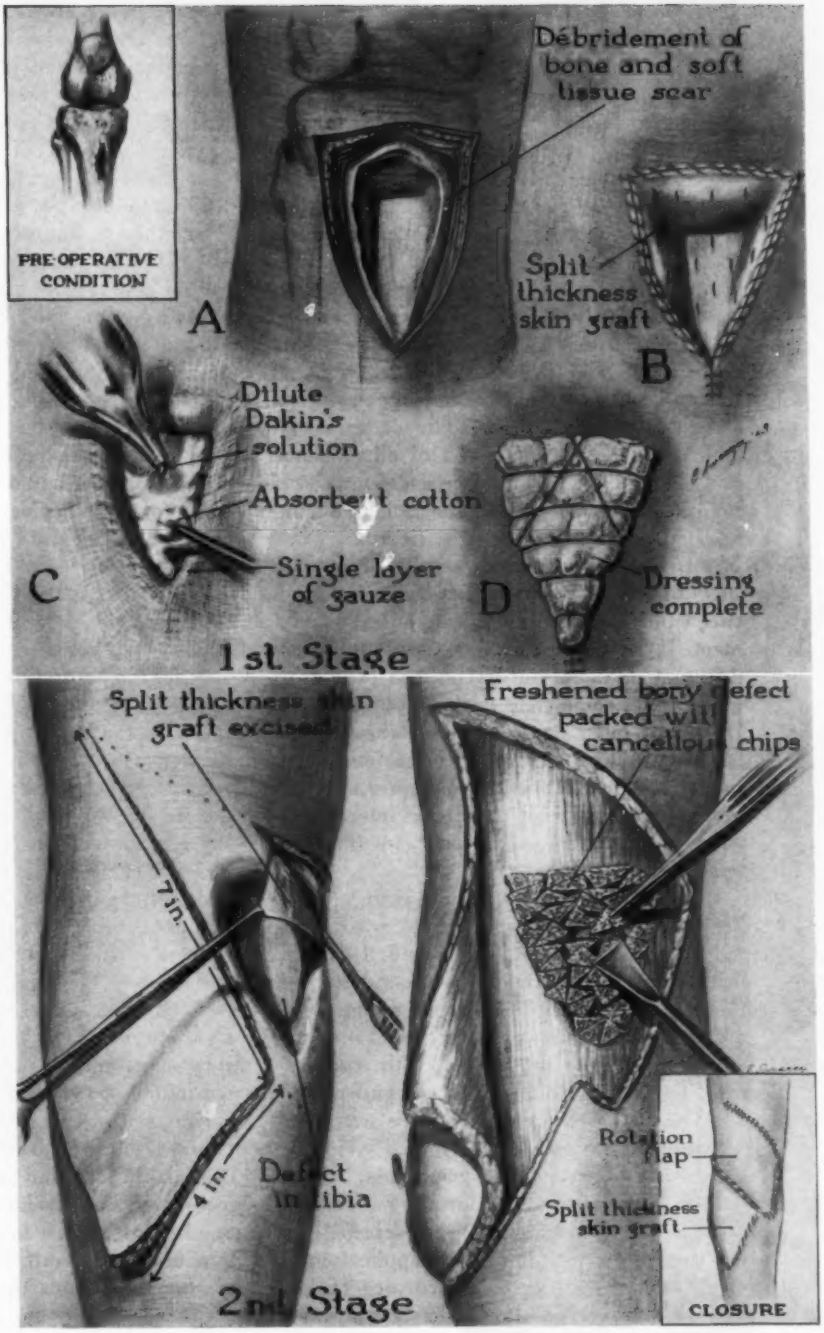

FIGURE 1. Radical excision of bone and soft tissue and application of split-thickness skin graft.

FIGURE 2. Removal of split-thickness skin graft. Freshening of defect, packing of cavity with cancellous bone, and closure with overlapping pedicle graft.

Figures 1 and 2 from SHANNON, J. G. and WOOLHOUSE, F. M.: Treatment of chronic bone infection. J. Bone & Joint Surg. 36A:841-850 (July) 1954. Reproduced courtesy of *The Journal of Bone and Joint Surgery*.

it is the most satisfactory form of treatment. We shall report the results of its use in the management of two types of compound fracture: (1) fresh fractures with extensive contamination, damage to soft tissue, and skin loss, and (2) recent compound fractures in which infection has developed. Our series is small but we believe it warrants consideration.

In the management of compound fractures it is of paramount importance to prevent infection. If the wound is small, and from within out, and if the delay between injury and treatment has not been long, careful excision and suturing of the wound are sufficient. If the wound is large and the damage extensive, the problem is much more difficult. In such a case we believe the excision of all damaged and contaminated tissue, free excision of skin margin, and immediate application of a split-skin graft constitute the best treatment. Use of a free skin graft simply as a "viable dressing" affords an advantageous compromise between the open and closed methods of treatment. If the debridement is adequate and an infection does not supervene, the skin graft takes and a completely healed wound results. If, on the other hand, any devitalized tissue has been left in the wound or serious infection supervenes, a portion of the graft will be lost but there will not have been interference with drainage. The following cases illustrate this principle.

Case 1—A 35 year old white man, a member of the Canadian armed forces, was admitted to the hospital on September 8, 1953, because of a self-inflicted gunshot wound through the lower part of the left leg. Examination revealed a severe compound fracture of the tibia and fibula at the lower third, with extensive soft-tissue damage and skin loss (figures 3 and 4). The foot was warm and there was good sensation in the sole of the foot. Psychiatric diagnosis was paranoid schizophrenia.

Four hours after admission the patient was taken to the operating room and debridement was carried out with immediate application of a split-skin graft to the denuded area (figure 5). The skin graft took completely and infection did not develop. In November 1953 the patient was advised to have a bone graft, but he refused. In May 1954 he consented to have a bone graft, and this was done on May 5. A bone-bank cortical graft was inserted across the fracture site and ankle joint. Cancellous chips obtained from the bone bank were packed about the cortical graft (figures 6 and 7). When the patient was last seen in May 1955, union was progressing satisfactorily. Since then he has refused to return to the hospital, but his wife reports that he is bearing full weight without complaint and is working.

Comment—This was a very extensive wound in a very uncooperative patient. We feel that this method of treatment helped materially in preventing infection and aiding the healing process.

Case 2—A 22 year old white man was admitted to the hospital on May 22, 1955, after an automobile accident. He had a compound comminuted fracture of the left tibia and fibula (figure 8). There was a large, badly contaminated wound at the fracture site. He also had a comminuted fracture of the right tibia and fibula and a comminuted fracture of the midshaft of the left radius.

Six hours after the accident the patient was taken to the operating room. The wound of the left leg was thoroughly debrided and a split-skin graft applied. The graft took completely. A full-thickness graft was applied to the fracture site on the left tibia on October 3, 1955 (figure 9). On December 1, 1955, a sliding bone graft with cancellous bone chips was applied. At this time the fracture of the right tibia showed little new bone formation. On January 17, 1956, the plate was removed from the tibia and a sliding bone graft applied. By June 1956 the fracture of the left tibia showed solid union but the right tibia still was not united (figure 10).

Comment—This was another case of compound fracture with extensive damage of soft tissue, skin loss, and gross contamination. Infection did not develop, and we think this was due in part at least to the immediate application of a skin graft after thorough debridement of the wound.

Case 3—A 19 year old white man was admitted to the hospital on May 22, 1955, after an automobile accident. He had bilateral se-

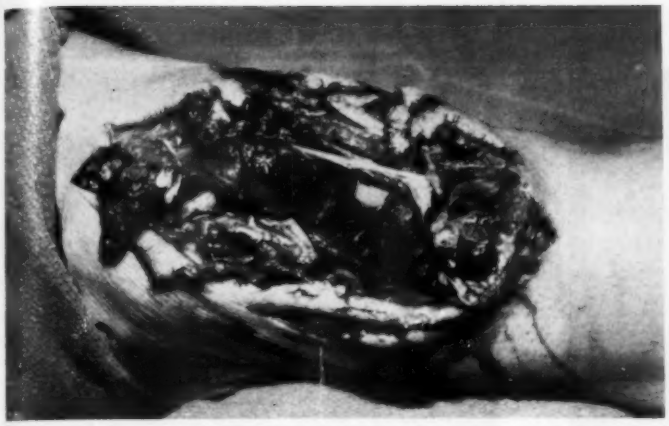

FIGURE 3 (case 1). Extensive through-and-through wound in the lower third of left leg.

FIGURE 4 (case 1). Extensive compound fracture of tibia and fibula.

FIGURE 5 (case 1). *Top.* Skin graft in place before the application of pressure dressing.

FIGURE 6 (case 1). Healed split-thickness skin graft.

FIGURE 7 (case 1). Bone grafts in place and union progressing satisfactorily. Final x-rays could not be obtained.

FIGURE 8 (case 2). Extensive compound fracture of left tibia and fibula.

FIGURE 9 (case 2). Final covering of the area with full-thickness skin and subcutaneous tissue.

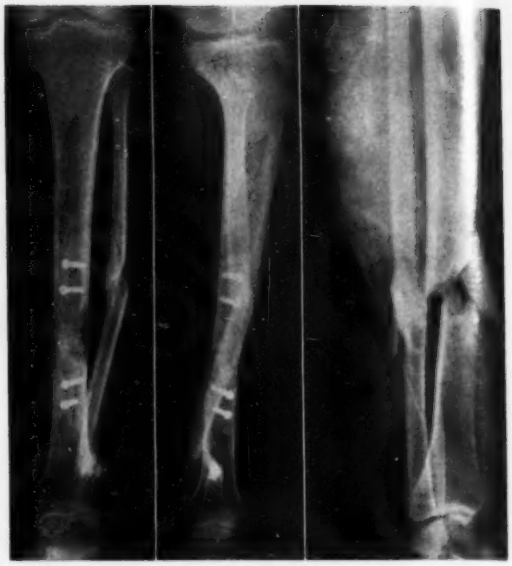

FIGURE 10 (case 2). Tibia at the time of solid union.

FIGURE 11 (case 3). Compound fracture of left tibia.

FIGURE 13 (case 3). Solid union of tibia.

FIGURE 12 (case 3). Full-thickness graft in place.

vere compound fractures of the tibiae and fibulae (figure 11).

Eight hours after admission the patient was taken to the operating room. The right leg was amputated below the knee. The wound in the left leg was thoroughly debrided. This left a large denuded area over the lower tibia at the site of fracture, which was covered immediately with a split-skin graft. The graft took almost completely. A pedicle skin flap from the abdomen was started on September 26, 1955, and completed on December 12, 1955. On January 5, 1956, a sliding bone graft with cancellous bone chips from the ilium was applied to the fracture. On July 15, 1956, the patient began weight bearing using a right prosthesis (figures 12 and 13).

Comment—Since it was necessary to amputate the right leg below the knee immediately, it was most important to reduce to a minimum the hazards to the left leg. Covering the denuded area with split-skin graft greatly reduced the risk of infection.

As a result of our experience with this method of treatment of chronic bone infection we have come to the conclusion that if infection has developed in a recent fracture the surest way to eradicate it is to apply the same method to the infected area. The following cases illustrate this point.

Case 4—A 31 year old man was admitted to the hospital on July 3, 1948, after a motorcycle accident. He had severe head injuries, a transverse fracture of the lower third of the left femur, laceration into the left knee joint, compound fracture of the lower third of the left tibia and fibula, avulsion of a flap of skin from the left heel, and multiple lacerations of both the right arm and the shoulder. He was unconscious.

The wounds were debrided and loosely closed. Kirschner wires were inserted at the tibial tubercle and os calcis, and the fractures were treated by traction in a Thomas splint. Definitive treatment had to wait until the end of July because of the patient's serious cerebral condition. Indeed, during most of this period it did not look as if he would survive. On July 20, 1948, a bone plate was applied to the fracture of the left femur. On August 20, 1948, because of infection at the fracture site in the left tibia, excision was done and a split-skin graft applied. The graft took well. On December 14, 1948, a sliding bone graft was applied at the fracture site of the left tibia. There was delayed union of the fracture of the left femur, necessitating a bone graft on May 3, 1949. At that time the tibial fracture showed no sign of infection and union was progressing satisfactorily. Recovery was further delayed by a re-fracture of the femur on November 30, 1949. However, the left tibia was soundly healed at that time.

Comment—In the light of more recent experience we think that the application of a split-skin graft to the tibial fracture site at the original operation might well have prevented infection.

Case 5—A 74 year old white man was admitted to the hospital on September 20, 1952. He had sustained a compound fracture of the lower third of the right tibia and fibula on July 31, 1952. There was a suppurating wound at the fracture site. On October 2, he was taken to the operating room and the infected area was excised, including the devitalized bone ends. A split-skin graft was applied, Kirschner wires being inserted at the tibial tubercle and above the ankle. These were incorporated in a plaster cast extending from toes to groin. In two weeks the wound was examined through a window in the cast. The graft had taken completely and the infection seemed to have been eradicated. The cast was changed and the wires were removed on November 28, 1952. It was thought that a bone graft probably would be necessary, and this made a full-thickness skin covering essential. An attempt was made to create a pedicle-skin graft from the abdomen, but this was abandoned because of necrosis of the tube. By this time, however, healing of the fracture was progressing satisfactorily. X-rays on May 28, 1953, showed firm union of the fracture (figure 14).

Comment—This case was very interesting in that there was gross infection at the fracture site and it was anticipated that a bone graft would be necessary when the infection cleared. However, when the infection was

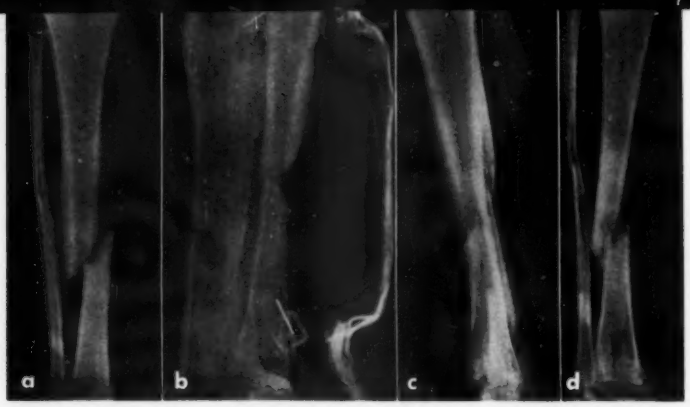

FIGURE 14 (case 5). a. Fracture at time of admission. b. Fracture in place after debridement and skin grafting. c and d. Healed fracture.

eradicated by excision and skin grafting, the fracture went on to firm union without further procedures.

Case 6—A 27 year old man was admitted to the hospital on October 3, 1952, because of infection at the site of a fracture of the left tibia and fibula, and nonunion. He had sustained the compound comminuted fracture on December 30, 1951. It had been treated by open reduction and plating the following day. In May 1952 he had been allowed to bear weight. Soon afterward, angulation at the fracture site had been noted and x-rays had revealed a break in the bone plate and nonunion. On July 8, 1952, the bone plate had been removed and a cortical graft inserted across the fracture site.

On November 12, 1952, after admission to this hospital, the fracture was exposed and the scarred and infected tissue was removed. The bone graft was found to be incorporated into the proximal fragment but not into the distal fragment. It was thought that the graft could be saved. Accordingly, parts of it that did not appear perfectly healthy were excised, and most of it was left in place. A split-skin graft was applied. This was a mistake, because the infection was not eradicated; it flared up postoperatively and the skin graft sloughed. On December 4, 1952, the procedure was repeated, and this time a more thorough excision of the involved bone was done. Following this procedure, the skin graft took well except at the lower end where a discharging sinus developed. Bony union progressed satisfactorily, and in May 1953 union was firm and weight bearing was allowed. The sinus continued to discharge occasionally. It was thought that the split-skin graft should be replaced with a full-thickness graft, and this was completed in June 1953. However, a sinus at the lower end of the wound persisted and continued to drain occasionally in spite of a further attempt to excise it in September 1953. The fracture remained firm and the patient has worked steadily since September 1954.

Comment—This case represents a failure of treatment, due to our failure to perform a complete radical excision at the time of the first operation.

Summary

Six cases of fracture of the leg are presented. In three there was gross contamination with extensive soft-tissue damage and skin loss. These were treated immediately by thorough debridement and application of split-skin grafts to the denuded areas. Infection did not develop. The other three were cases of recent fractures in which infection had developed. These were treated by excision of the infected area and application of a split-skin graft. In two cases the infection was quickly eradicated, but in the third the infection did not clear completely. This was due to failure to perform a sufficiently radical excision.

This series is much too small to permit any definite conclusions to be drawn, but we have been very impressed with this method and present it as a useful means of dealing with such cases.

REFERENCE

1. SHANNON, J. G. and WOOLHOUSE, F. M.: Treatment of chronic bone infection. J. Bone & Joint Surg. 36A:841-850 (July) 1954.

A study of 38 cases of idiopathic hypercalcemia suggests that the etiologic factor concerned is the intake of vitamin D. Clinical symptoms, which include anorexia, constipation, listlessness and thirst with polyuria and slight dehydration, are similar to those of hypervitaminosis D. Biochemical findings are also those of such a diagnosis. Recommended treatment includes omitting all vitamin D from the diet and use of a low calcium milk until serum calcium returns to normal.

Idiopathic Hypercalcemia

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DURING the past two or three decades, descriptions of several new syndromes have been added to pediatric literature. Whether these are in fact new or only newly recognized is a moot point. Evidence would seem to show that what has been called idiopathic hypercalcemia, if not a new disease, has become a much more common biochemical finding than it used to be. Until recently it was a rare condition for which there was usually a satisfactory explanation such as hyperparathyroidism, either primary or secondary, sarcoidosis, hypervitaminosis D, the milk and alkali syndrome, or osteoporosis occurring in disease atrophy. It has been stated that hypercalcemia is also found in interstitial plasma cell pneumonia,[1] but we have not observed such cases; from a study of those reported, however, it would seem likely that in some, if not in all, hypervitaminosis D could not be ruled out.

In 1952 Lightwood and Payne[2] described a syndrome occurring in infants which resembled to some extent hyperchloremic acidosis as described by Lightwood in 1935 but in which there was hypercalcemia. This article deals briefly with observations from a study of 38 cases belonging to the latter group. The patients were seen at the Royal Hospital for Sick Children, Glasgow, during the period from 1951 to 1957. The study does not include cases such as those described by Fanconi[3] in 1951 and by Schlesinger, Butler and Black[4] in 1952, in which there were associated abnormalities such as microcephaly, mental deficiency, congenital heart disease, hypertension and osteosclerotic bone changes. This "severe" type is rare, and in the present state of our knowledge it is uncertain what relation, if any, it bears to the type under discussion, which presents a recognizable clinical picture.

Clinical Observations

The ages of the 38 patients at the onset of the hypercalcemic condition varied from three weeks to 11 months. None of the infants were

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FIGURE 1. Infant, age 10 months, showing facies in hypercalcemia.

breast fed at the time. The onset as a rule was fairly sudden, the story being that of the development of anorexia, vomiting, loss of weight and, of course, constipation in an infant who had been thriving. Thirst was an important symptom, occurring in 19 of the 38 cases, and polyuria was seen less often. Vomiting, constipation and anorexia were more frequent symptoms than thirst (occurring in 37, 33 and 19 cases, respectively) but, because they are common to so many diseases, were of less diagnostic significance. Also, specific inquiries about thirst were probably not always made. Constipation, often a source of worry to the mother, was much more intractable than usual. Hard fecal masses were as a rule readily palpable in the left iliac fossa. The anorexia was characterized by a refusal of solids and semisolids more than of fluids, but nevertheless resulted in considerable dehydration and loss of weight in some cases.

Intake of vitamin D was on the whole far above the average requirements. The vitamin was given soon after birth until the condition was recognized. Intake varied from 200 to 8800 I.U. per day. Twenty-eight of the infants received over 1000 units, 12 over 2000, three over 4000, and eight under 1000 units. In two cases there was no history of vitamin D intake either as such or in the milk. It may be significant that 27 of the 38 infants received the vitamin as vitamin D_2. The infants who had received in part vitamin D_3 had never been given more than 400 units.

Few abnormalities were noted on physical examination. Perhaps the most important finding was the presence of a certain amount of wasting and of slight dehydration. The infants were apathetic but not irritable, the lips were dry, the eyes were slightly sunken, and the muscle tone and tissue turgor were generally poor (figure 1). These manifestations were seldom, if ever, severe enough to cause alarm. The abdomen tended to be scaphoid, and

scybalous masses in the colon were easily palpable.

Fever was not a feature, and infection other than that found in the urinary tract was uncommon. Eleven of the 38 infants had mild pyuria, which was peculiarly resistant to treatment and tended to recur with a different causal organism.

The severity of the signs and symptoms bore no relationship to the level of the serum calcium, nor did improvement necessarily take place when the serum calcium returned to normal. Indeed, it was noted that improvement might be delayed several weeks, and if treatment is omitted too soon the serum calcium level might become elevated again within a week or 10 days.

Biochemical Observations

The clinical picture was such that a provisional diagnosis of hypercalcemia was often made in the outpatient department to be confirmed later by the finding of a serum calcium of over 12 mg. per 100 ml. For a period, routine serum calcium estimations were made on all infants under one year of age admitted to the wards, and a few unsuspected cases were found.

Taking the highest values obtained in each case, the serum calcium was over 14 mg. per 100 ml. in 20 cases and over 16 mg. in three. The highest value obtained was 18.6 mg. in an infant seven months of age whose intake of vitamin D (all as vitamin D_2) was estimated at 1,320 I.U. per day and who made a complete recovery.

Serum phosphorus was slightly higher than the average, ranging from 3.2 mg. (one case) to 7.6 mg. per 100 ml. In 21 of the 30 infants in whom it was estimated, the level was over 5 mg., and in four it was over 7 mg.

Calcium and phosphorus balance studies have been carried out in three of the cases (table 1), and in none could the retentions be regarded as high. Indeed, if one accepts the average daily retention of calcium as being 0.04 to 0.06 gm. per kilogram of body weight per day (or 30 to 50 per cent of the intake), the retention in one of the infants (M. R. 1) was definitely low. The retentions of phosphorus gave similar values. Urinary output of phosphorus was high. Hypercalciuria was found in only four of the 14 cases in which the calcium output in the urine was estimated. The upper limit of normal was taken as 85 mg. per day.

The blood urea (or nonprotein nitrogen) was usually but not invariably increased and never to very high levels. In 26 cases it was over 40 mg. per 100 ml. The highest value obtained was 87 mg. Contrary to the findings of some other workers, the serum proteins were not consistently high. In 10 cases they were over 7 gm. per 100 ml., the highest being 8.8 gm.

There is considerable difference of opinion as to the level of cholesterol found in the blood. Forfar and associates[5] expressed the belief that it is consistently high and that this is due to a rise in the free fraction. They found a correlation between the levels of plasma cholesterol and serum calcium. Unfortunately in our series the cholesterol was estimated by more than one method. In the earlier cases using chloroform or ether and alcohol extraction, the values fell within the accepted range. Using the direct method of Zlatkis, Zak and Boyle[6] and accepting 250 mg. per 100 ml. as the upper limit of normal, in four cases out of 12 the level was found to be high. The highest level obtained was 336 mg. per 100 ml.

Association With Renal Acidosis

In addition to the 38 cases of idiopathic hypercalcemia, there were also nine cases of hypercalcemia complicating renal acidosis during the same period. The clinical picture was much the same as that described for idiopathic hypercalcemia but the total carbon dioxide content of the plasma was diminished and the chloride correspondingly increased.

The significance of this finding is not apparent, but it would appear to be more common than is suspected. In fatal cases, renal calcinosis has been a finding common to both diseases, and this would point to some common etiologic factor such as a renal tubular defect either congenital or acquired. It is worthy of comment that in this hospital renal acidosis uncomplicated by hypercalcemia is

TABLE 1

RETENTIONS OF CALCIUM AND PHOSPHORUS IN IDIOPATHIC HYPERCALCEMIA*

PATIENT	AGE (Months)	WEIGHT (Kilograms)	DAILY INTAKE		DAILY OUTPUT				DAILY RETENTION PER KILOGRAM OF BODY WEIGHT		PER CENT OF INTAKE RETAINED		REMARKS
					FECES		URINE						
			Ca	*P*	*Ca*	*P*	*Ca*	*P*	*Ca*	*P*	*Ca*	*P*	
W. M.	10	8.5	1.452	1.065	0.958	0.342	0.105	0.455	0.046	0.032	27	25	Cow's milk, six day period
			0.060	0.440	0.184	0.072	0.051	0.324	−0.029	0.005		10	Low calcium milk, six day period
M. R. (1)†	8	9.5	1.204	0.931	0.970	0.425	0.050	0.310	0.020	0.020	15	21	Cow's milk, five day period
M. R. (2)†	8	6.7	0.902	0.723	0.427	0.115	0.058	0.257	0.062	0.052	46	48	Cow's milk, seven day period

*Expressed in grams.

†Twins.

I am indebted to Dr. S. MacBean for these estimations.

very rarely seen, and furthermore hypercalcemia has been much less frequent during the past six months than previously although serum calcium estimations have been made on every infant in whom there has been suspicion that the condition may have been present. In this connection it is perhaps significant that the vitamin D in cod liver oil has been reduced to 100 units per gram instead of 200, and the vitamin D in dried milk from 280 units to 100 units per dry ounce of powder.

Treatment

Three methods of treatment have been used: omission of all vitamin D from the food, use of a low calcium milk (available commercially in Great Britain), and use of cortisone.

Omission of vitamin D is a slow, relatively ineffective treatment, and in view of the possible dangers attached to a persisting medullary renal calcinosis, which presumably all show in some degree, it cannot be recommended. Cortisone or prednisolone caused a rapid return to normal of the serum calcium in all but one of the cases in which it was given. Reduction of calcium intake by use of a low calcium milk is undoubtedly the most effective way of bringing the serum calcium back to normal, but it also produces a negative calcium balance (table 1), and should therefore be used cautiously and not for long periods. As previously mentioned, even after the serum calcium returns to normal the general condition of the child improves very slowly, and it is not easy to say when cure is established. In the light of our present knowledge it is suggested that treatment should consist of the omission of all vitamin D from the diet and the use of a low calcium milk until the serum calcium returns to normal. This takes from 7 to 10 days. Thereafter calcium can be introduced by changing over gradually to ordinary liquid or dried milk. The serum calcium must be estimated at intervals until the risk of hypercalcemia no longer exists. On an average the duration of the disease is from two to four months. The usual protection against infection while the infant is in the hospital is essential, and for obvious reasons dismissal to the home as soon as possible is recommended.

Discussion

Of the known causes of hypercalcemia, only the milk and alkali syndrome and hypervitaminosis D need be considered.

Forfar and associates[5] suggested that there is a disturbance of cholesterol metabolism probably induced by infection. They found that the serum citrate level and the urinary output of citrate were both low during the active stage of the disease, a finding in contrast to the high figures usually obtained in hypervitaminosis D. They also noted that a low calcium intake induced a negative calcium balance and lowered the level of the serum calcium to normal without necessarily causing clinical improvement.

Creery[7] suggested a parallel with the milk and alkali syndrome, described by Cope[8] as occurring in patients with peptic ulcer on treatment with large intakes of milk and alkali and in whom the serum calcium, serum phosphorus and blood urea are raised. In six cases Creery found evidence of overdosage with alkaline preparations producing a slight degree of alkalosis. This he believed depressed the renal function, which caused in turn a rise in the serum calcium and serum phosphorus. In another article, written with Neill, however, Creery[9] was unable to confirm these observations. Alkalosis may occur in infants with high intestinal obstruction (pyloric stenosis) or in older children with poor renal function following alkali administration, and although the total serum calcium may rise slightly, as it does in gastric tetany, levels of 12 mg. per 100 ml. are seldom found.

Broadly speaking, the clinical picture of idiopathic hypercalcemia, namely, anorexia, listlessness, constipation and thirst with polyuria and slight dehydration, is similar to that ascribed to hypervitaminosis D. Likewise the biochemical findings are in keeping with such a diagnosis—a raised serum calcium and serum phosphorus and an increased excretion of phosphorus in the urine. The latter finding is present even when the serum calcium has returned to normal following the use of cortisone or low calcium milk and can be taken as evidence that homeostasis is not achieved at once, and it provides an explanation of the persistence of the clinical picture in the presence of a normal serum calcium content.

In this series of cases, hypercalciuria was not found as frequently as it was in Forfar's cases, and it may be that our observations were not numerous enough. Presumably if nephrocalcinosis exists in all cases of idiopathic hypercalcemia (and this seems likely) excess calcium in the urine will be found at some stage of the disease just as it is in hypercalcemia occurring in sarcoidosis.

Balance studies (table 1) show that the calcium and phosphorus retentions were not increased to any extent and that the phosphorus was excreted principally in the urine. At first glance these findings may seem to be at variance with what should occur when vitamin D is given. One must remember, however, that the results of giving vitamin D will depend on whether the infant is rachitic or not. The infants with hypercalcemia were nonrachitic. In rachitic infants where the body is starved of these essential minerals, vitamin D results in a great increase in the retention of calcium and phosphorus and there is tubular reabsorption of phosphorus. In nonrachitic infants the retentions are not increased or at least not notably so, nor does the urinary phosphorus fall.[10]

Against the suggestion that idiopathic hypercalcemia is due to overdosage of vitamin D is the fact that in some instances the intake of vitamin has not been excessive. Indeed, in two of the 38 cases no evidence was obtained that any had been given. It is also true that many infants on similarly large intakes remain well and do not show hypercalcemia. It has been suggested too that administration of vitamin D to infants after recovery from hypercalcemia does not induce another attack. The evidence that this is so is not convincing; it is unlikely that a single large dose or even a few doses over several days would be adequate. It would be necessary to give comparable large doses over a long period, and it is doubtful if this could be justified.

These arguments can be used to support the idea that infants with hypercalcemia are in some peculiar and unrecognized way more

sensitive to vitamin D than other infants. This may well be true. If certain infants can be resistant to vitamin D, there seems no difficulty in accepting the possibility of undue sensitivity. Certainly the severity of the clinical picture is not necessarily related to the height of the serum calcium level or to the intake of the vitamin.

One other suggestion may be made. It may well be that the ill effects arising from vitamin D therapy are more readily induced by vitamin D_2 (irradiated ergosterol) or the impurities contained in this synthetic vitamin than by the naturally occurring vitamin D_3 (7-dehydrocholesterol) found in animal fats. Proof of this would not be easily obtained. Most of the vitamin D given to infants is in the form of vitamin D_2, and overdosage with vitamin D_3 as it is found in cod liver oil is unlikely.

That the damage, including nephrocalcinosis, produced by excess vitamin D is reversible seems proved by the fact that the affected infants recover completely and that any death occurring during the hypercalcemic phase is the result of the infection which was the reason the infant was brought under observation in the first place.

Summary

The clinical picture of idiopathic hypercalcemia is described and evidence adduced that the etiologic factor concerned is the intake of vitamin D. The hypercalcemia is due to excessive intake, or the impurities which vitamin D_2 contains, or to hypersensitivity of the infant.

REFERENCES

1. Hjelt, L., Ahvenainen, E. K. and Hallman, N.: Renal calcifications in infancy. Autopsy findings in interstitial plasma cell pneumonia and other pathological conditions. Ann. paediat. Fenniae 2:69, 1956.
2. Lightwood, R. and Payne, W.: Idiopathic hypercalcaemia in infants with failure to thrive. The blood chemistry in idiopathic hypercalcaemia. Proceedings of the twenty-third general meeting of the British Paediatric Association. Arch. Dis. Childhood 27:302, 1952.
3. Fanconi, G.: Über chronische Störungen des Calcium und Phosphatstoffwechsels in Kindesalter. Schweiz. med. Wchnschr. 81:908, 1951.
4. Schlesinger, B., Butler, N. and Black, J.: Chronische Hypercalcämie, kombiniert mit Osteosklerose, Hyperazotämie, Minderwuchs und kongenitalen Missbildungen. Helvet. paediat. acta 7:335, 1952.
5. Forfar, J., Balf, C., Maxwell, G. and Tompsett, S.: Idiopathic hypercalcaemia of infancy; clinical and metabolic studies with special reference to the aetological role of vitamin D. Lancet 1:981, 1956.
6. Zlatkis, A., Zak, B. and Boyle, A. J.: New method for direct determination of serum cholesterol. J. Lab. & Clin. Med. 41:486, 1953.
7. Creery, R. D. G.: Idiopathic hypercalcaemia of infants. Lancet 2:17, 1953.
8. Cope, C. L.: Base changes in alkalosis produced by treatment of gastric ulcer with alkalies. Clin. Sc. 2:287, 1936.
9. Creery, R. D. G. and Neill, D. W.: Idiopathic hypercalcaemia in infants with failure to thrive. Lancet 2:110, 1954.
10. Houet, R.: Recherches sur le métabolisme du calcium et du phosphore dans l'enfance; effets de l'administration per os de 15 mg. de vitamine D sur les bilans du phosphore et de calcium chez le nourrisson. Ann. paediat. 166:177, 1946.

Almost every case of eclampsia is preventable. Prevention depends on prenatal care. The earliest possible detection of preeclampsia and of a rise in blood pressure is essential. Edema is the first warning sign; suggested treatment includes rest, minimum salt diet, and acetazolamide. Notification of eclampsia would be an effective weapon in reducing the incidence of the disease.

Could the Chapter on Eclampsia Disappear?

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DURING World War II, I had been asked to write a series of bulletins on "Obstetrics for the wartime graduate in the services." I mentioned to an obstetrician of ripe experience and a real love for prenatal care that my next bulletin would be on the treatment of eclampsia, something practical and necessary.

"Is it?" he asked laconically.

"Surely!" was my answer.

"I doubt it," he replied. "I've never had a case of eclampsia in my practice. With good prenatal care, the chapter on eclampsia could disappear."

This was in 1941. Ten years later what had been said of a large private practice was repeated in a large public practice. In 1951 at the Women's Hospital Crown Street, Sydney, as the result of an intensive prenatal campaign there was not a single case of eclampsia in over 4000 booked cases.

This notable achievement has been repeated in 1953, 1955 and again in 1956 (figure 1).

In the same year, however (1951), in the state of New South Wales (population in 1951, 3,318,800), 17 women *died* from eclampsia. How many cases occurred we do not know, nor do we know how close to death many of the women came, or the number of babies that were lost.

The text I give my students is *Eclamptics are like road accidents, mostly preventable.*

The crusade against eclampsia may sound tiresome to some, but one is constrained to feel that it is necessary when one reads the statement in a recent paper in a very good journal that "of ten patients whose pre-toxaemic state had been detected by a new prognostic pre-toxaemia test three became eclamptic in spite of prophylaxis."

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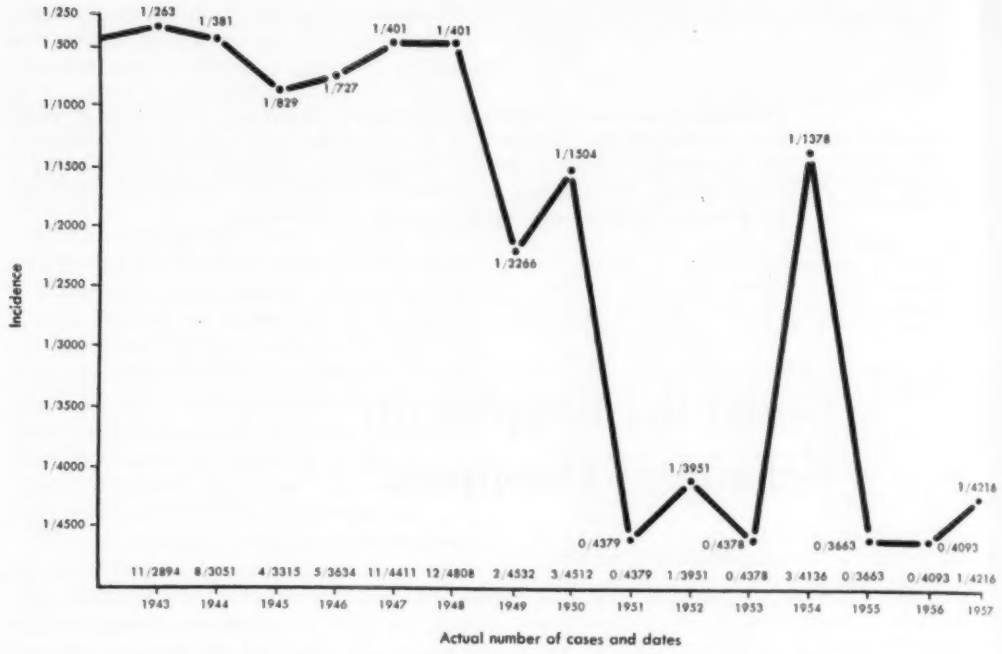


FIGURE 1. Incidence of eclampsia in booked patients at the Women's Hospital Crown Street, Sydney. The campaign to prevent eclampsia started 10 years ago (1948). Since then there have been only 10 eclamptics among 37,860 patients confined, while in four of the 10 years there was not a single case of eclampsia.

The positive aim of modern medicine is surely preventive, and few fields offer brighter prospects of immediate success in the prevention not merely of a horrible disease but of death itself. For eclampsia is one of the three chief causes of maternal death in many countries of the world, including Australia.

Now when one claims that good prenatal care can prevent eclampsia, one hastens to assure one's colleagues that this is not the impeachment of a hard-working, conscientious profession which carries an inordinate responsibility—that of people's lives. We would, of course, constantly examine our own standard of prenatal care but eclampsia can occur from lack of cooperation of the patient. Indeed during the 1951 Sydney campaign even the constabulary had to be called in on occasion to persuade a busy mother to keep her appointment at the prenatal clinic!

It is an extraordinary fact that one of the most difficult things in the world is to get people to try and save their own lives. Consider the appalling toll of road accidents and the ingenuity and skill devoted to producing the most effective missile for wiping out humanity.

But let us leave man to his end and return to his beginning, i.e., childbirth.

Let us state the problem: *Eclampsia in almost every case is a preventable disease* and yet eclampsia still occurs regularly and is in several countries, including Australia, the chief cause of maternal death.

Prevention means prenatal care. It means also a change of concept, a matter of thinking not of the treatment of eclampsia but of preeclampsia.

In Australia, and I would think generally, the problem is mostly of preeclampsia in the primigravida. Quite common also is the woman with chronic hypertension, while in a number a case of hypertension is complicated in the later months of pregnancy by the superimposition of preeclampsia.

Chronic nephritis is rare in the pregnant woman in Australia.

From a practical point of view the prevention of eclampsia therefore means earliest possible detection of preeclampsia.

The first warning is the *weight*. The text I give my students is *Weight is water*. So important do I believe the earliest detection of edema to be, that if a candidate in answer to the question, "What does excessive weight increase in a pregnant woman mean to you?" answers "Fat!" we spend a few months more together unlearning the error.

Excessive weight increase is regarded by some as of particular significance between the twentieth and thirtieth weeks. An increase of over 8 lb. in this period is regarded as a warning of the almost certain later manifestation of the full toxemic pattern.

It is a pity not to weigh your patient. I believe there are some who do not. I have never found any difficulty in interesting a woman in her weight—it is a strong link in the chain of cooperation, and women cooperate wonderfully even to the unpalatable salt-free diet.

Edema one suggests is present if the weight has increased by more than a pound per week. It may not be obvious to our crude clinical tests—pitting over the tibia and the tight wedding ring—but it is present in more vulnerable parts and notably in the kidney.

Edema inside a tight inelastic renal capsule must interfere with an efficient blood supply to sensitive renal tissue. Adding to ischemia and renal hypoxia the spasm of afferent arterioles to the glomeruli that occurs with the development of hypertension produces a pretty sick kidney. The pity of it is that the kidney does not complain until its condition is advanced to the stage where damaged capillaries weep tears of albumin.

Renal efficiency tests do not help the obstetrician. For many years I put the biochemist to trouble and the patient to expense in urea concentration and urea clearance tests. Today in assessing renal damage in pregnancy I regard them as valueless. Specific gravity and volume of urine passed are of importance while the blood urea, repeated of course, is a useful indication of mounting renal damage.

Treatment of the Edema

The most effective measures I have found are rest, minimum-salt diet, and acetazolamide (2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide) (DIAMOX®).

Rest—Rest is such an unimpressive prescription. In the modern neotherapeutic days of specific antibiotic and other measures we are still tied to the paleotherapeutics of ignorance of the cause of the toxemia.

There is a small old book called "Rest and Pain" by John Hilton, first published back in 1863. If you have not read it, I envy you, for you have something to look forward to.

Nearly 100 years ago Hilton addressed the Royal College of Surgeons of England. He took as the subject of his lecture "Rest." "So apparently simple," he said, "as to make me almost apologize to you for selecting it."

I should like to revive his subject—the recuperative power of nature—it could possibly be overlooked as a factor in recovery from disease. If kept in mind it could save a lot of antibiotics and the disturbing resistance of once-sensitive organisms built up by the abuse of these drugs.

Hilton's words are worth recalling. "Rest is essential to growth. We recognise this in the growing child where the one who sleeps most, usually thrives . . . while the wakeful, restless child seldom displays the evidence of active nutrition.

"What is true of growth is true also of repair. Repair is but the repetition of growth. The same elements, the same kindred conditions are necessary to the same results."

Rest is a diuretic. Moreover it is educational. For the average active woman with toxemia, rest is very much a relative term. It must be in a hospital, and there is no doubt of its effect on the psyche and the soma if impressed on the patient "early in the piece."

I recall a woman who married at 35 and soon became pregnant. At "30 weeks" edema and hypertension developed. She had led an intensely busy secretarial and nursing life for many years. When I suggested rest as essential if she were to carry through she replied that she could do that at home. After all she had

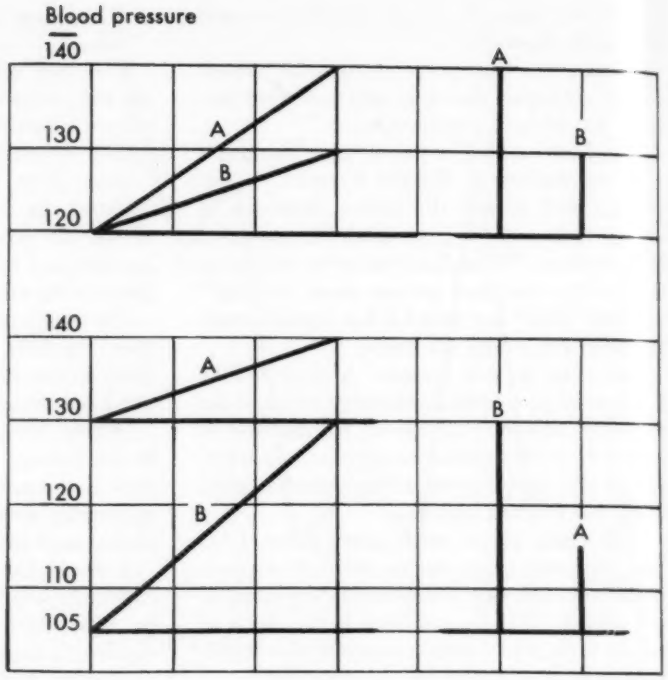


FIGURE 2. Relativity of blood pressure (after the late T. Dixon Hughes). See text.

been a nurse and understood exactly what I meant! Two weeks at home had no effect on the hypertension and so to the hospital she came. Now the odd weed in the garden got a chance to grow and the dust to collect under the furniture. But what was important was that the blood pressure came down, eclampsia was prevented, and she got a living baby. Rest is hard work for an active mind which has to be educated down to it.

Acetazolamide (Diamox)—This sodium-excreting drug has been, in our experience, a most effective diuretic and sodium excretor. In all patients it caused a considerable increase in the sodium excretion in the urine, the average being a fourfold rise in the daily output. Total urinary volume rose correspondingly. It is a useful ancillary to rest and diet.

Blood Pressure

In the prevention of eclampsia the earliest possible detection of a rise in blood pressure is an absolute essential. Two important aspects of blood pressure are: (1) What is a rise? and (2) the relativity of the blood pressure.

I am convinced that if we are sincerely concerned with prevention of eclampsia we must regard as the upper limits of normal in pregnant women 120 mm. Hg systolic and 80 diastolic. I realize that some will oppose this standard, saying that it automatically classifies many normal women as hypertensive. If the antagonist would substitute for "normal women" the words "pregnant women" and particularly primigravidas, I would agree.

It is unfortunately too true if the experience of the "Sydney experiment" (as I have heard the antieclampsia campaign called overseas) has a lesson, it is in a really critical regard for the blood pressure levels.

I overcome the difficulty of two opposing opinions by having two standards of blood pressure—one for the pregnant woman and one for the other citizen. After all, is this unreasonable? The pregnant woman is entitled to a standard of her own; firstly she's a woman, secondly a woman in a particular age group, and thirdly she is a pregnant woman.

TABLE 1

ECLAMPSIA IN NEW ZEALAND

PERIOD	TOTAL BIRTHS	CASES OF ECLAMPSIA	MATERNAL DEATHS	MATERNAL MORTALITY RATE
1928-1933	157,264	491 (3.2 per 1000)	93 (0.6 per 1000)	18.9%
1953-1955	164,629	206 (1.25 per 1000)	5 (0.03 per 1000)	2.4%

And that leaves others such as the middle-aged man with a blood pressure of 180/100 much happier with his state!

The second aspect of the blood pressure is relativity. The concept should be not that "the blood pressure has risen to 140 or 150" but that "it has risen 10 or 15 mm."

The late Dr. T. Dixon Hughes, who played a major role in the "Sydney experiment" in 1951, used to demonstrate this point well by his diagrams, which I am privileged to reproduce (figure 2).

In the top record Mrs. A. has gone from 120 to 140 mm. Hg (a rise of 20 mm.), Mrs. B. only from 120 to 130 (a rise of 10 mm.). They both started from the same level. Mrs. A. is worse than Mrs. B.

But in the lower record Mrs. B. starts from a level of 105 mm. (not uncommon in early pregnancy); by rising to 130 mm. she has risen 25 mm., whereas Mrs. A., starting from 130 mm. has risen by only 10 mm. to reach 140 mm. Although the blood pressure is higher absolutely, Mrs. A. has not deteriorated, toxemically speaking, as much as Mrs. B.

Elementary, you will say, and I agree, but you will, I am sure, bear with me when I recall that *women under supervision are still having eclampsia* and that eclampsia means death to some women and to many more babies.

Prevention lies in the earliest possible detection. These earliest signs are weight and blood pressure.

Notification of Eclampsia

There is another weapon we can use against the eclamptic enemy. I realize that the mention of another "form" to be filled in often evokes justifiable opposition from the hard-working doctor. But if we ponder for a moment, with eclampsia made a notifiable disease, it could be that a doctor would complete his professional life without ever having had to fill in a single eclampsia form. At most, the number of such forms he would require would be very small because, let us remember, the condition is almost always preventable.

The suggestion is not therefore the academic idea of a cloud-cowled professor living in the attic of an ivory tower. Like yourself, I am happy to know that I carry the responsibility of intimate management of these patients. Moreover, one did not graduate to a chair of obstetrics through any academic hothouse, but from the ranks of the general practitioner, and I am grateful for that experience. It keeps your "feet on the ground"; there is no room for theory at the bedside.

Notification of eclampsia has been a fact for 32 years in New Zealand. The one mostly responsible for the administration of the scheme is a very fine obstetrician, Dr. T. F. Corkill of Wellington, New Zealand.

Its effect in reducing the incidence of eclampsia has been remarkable, and as a grain of experience is worth a ton of precept, I have sought Dr. Corkill's permission to tell you the results and a few of his observations.

The first comment is a reassurance to our colleagues. He says, "The reports of cases are strictly confidential and used solely for scientific research. Knowing this, medical practitioners give almost 100 per cent cooperation."

He continues, "It can be fairly claimed that we have as accurate a knowledge of the eclampsia position in New Zealand over 32 years as is available for any country in the world."

These are the facts (table 1):

1. Incidence—The incidence of eclampsia in New Zealand was reduced from 3.2 per 1000 births in 1928 to 1933 to 1.25 per 1000 in 1953 to 1955.

TABLE 2

TOXEMIA DEATHS IN DIFFERENT PARTS OF THE BRITISH COMMONWEALTH OF NATIONS OVER PERIOD 1953-1954

COUNTRY	TOTAL BIRTHS	TOTAL TOXEMIA DEATHS	ECLAMPSIA DEATHS	AREA (SQUARE MILES)
England and Wales	1,358,023	290 (0.21 per 1000)	142 (0.10 per 1000)	58,343
New Zealand	108,065 (European and Mauri)	27 (0.25 per 1000)	4 (0.04 per 1000)	103,736
Victoria (Australia)	108,221	18 (0.17 per 1000)	7 (0.06 per 1000)	87,884
New South Wales (Australia)	148,015	22 (0.15 per 1000)	4 (0.03 per 1000)	309,433

2. Maternal deaths—The maternal deaths from eclampsia have been reduced from 0.6 per 1000 births to 0.03 per 1000—a twenty-fold improvement and *a saving of mothers' lives that no words can adequately describe.*

3. Infant mortality—Stillbirths and neonatal deaths have fallen from 42 per cent to 17.7 per cent, and this, of course, in a greatly reduced number of cases.

It is instructive to compare the records over a recent quarter-century, remembering that prenatal care has been a fact only over the past half-century.

1. There has been a steady increase in the *percentage of mild cases* of eclampsia over the years. Indeed over 60 per cent of the cases of eclampsia that have occurred have been of the very mild type. (The criterion taken of a "very mild case" was "three fits or less and survival of both mother and infant.")

2. In an increasing proportion of the patients in whom eclampsia develops now, it does so *in the postpartum period or in the late second stage.*

This is obviously the result of better prenatal care, driving the eclamptic army, if not completely off the battlefield, at least into dismembered fragments of a weakened force.

Comparison of international statistics is always difficult. When it comes to eclampsia it is well-nigh impossible because in most countries (to my knowledge) eclampsia is not a notifiable disease. Eclamptic *deaths* are certainly recorded, but except for New Zealand the number of eclamptics in British countries without notification is probably impossible of assessment. I am pleased, however, to report that with the support of one's colleagues who believe in the preventability of eclampsia, success came in 1955 in having the National Health and Medical Research Council of Australia (the highest public health authority in the country) recommend that eclampsia be made a notifiable disease.

The implementation of this depends on the individual departments of health in each of the six Australian states. It is to be regretted that so far the Council's recommendation has not been implemented, but I am confident that it will come because the machinery is moving in one or two states to alter the relevant Act of Parliament.*

In the meantime it might be interesting to study, as far as possible, the state in different parts of the British Commonwealth of Nations (table 2). I stress that it is not an attempt at comparison. So many factors influence the figures such as geographical and climatic conditions, affecting accessibility to prenatal clinics and hospitals. But allowing for these and possibly other variants, the figures for New Zealand and New South Wales give us food for thought. Prenatal care is, of course, the basic factor; I think the other factors at work must have been in New Zealand notification of eclampsia, and in New South Wales the effect of the Sydney (Women's Hospital Crown Street) "experiment." In New South Wales a further factor has been the work of the Special

*Since this paper was prepared the Western Australian government has proclaimed regulations under the Health Act requiring the notification of eclampsia.

Medical Committee for Investigation of Maternal Mortality (State Health Department) which has been in existence now for 19 years. It meets monthly and considers maternal deaths in the whole of New South Wales, classifying them as to their preventability. The Committee has developed a free consultation service and has made two five year surveys.

Uterine cancer and eclampsia are always closely associated in one's mind because they are two of the most common causes of maternal death. (It is well known that uterine cancer is much more frequent in women who have had babies.) *In both, the key to successful treatment is the earliest possible detection.* In one, the *Papanicolaou smear* allows us today to speak of a "preventable cancer"; in the other, it is *prenatal care.*

We have two valuable instruments of modern preventive medicine. It is doubtful if full use is being made of them.

ACKNOWLEDGMENT

I acknowledge with appreciation the assistance, in the compilation of the statistics in this paper, of Dr. G. Cuthbert-Browne, Director of Maternal and Baby Welfare, Department of Public Health, New South Wales, of Dr. H. O. Lancaster, Senior Lecturer in Medical Statistics, University of Sydney, and of Dr. T. F. Corkill, Wellington, New Zealand.

REFERENCES

1. Hughes, T. D.: Adequate antenatal care and the prevention of eclampsia and severe toxemia. M. J. Australia 2:616 (October) 1955.
2. Corkill, T. F.: Eclampsia—changes in pattern. J. Obst. & Gynaec. Brit. Emp. 54:67, 1957.
3. Raab, W.: Prognostic pretoxemia tests in pregnancy. Am. J. Obst. & Gynec. 74:1048, 1957.
4. Medical and Clinical Report, The Women's Hospital Crown Street, Sydney, 1955-1956.
5. Annual Reports of the Registrar-General for England and Wales.
6. Manual of International Statistical Classification of Diseases, Injuries and Causes of Death. World Health Organization, 1957.
7. Demography: The Annual Bulletin of Bureau of Census and Statistics, Canberra, Australia.

Postgraduate Clinical NOTES

107. THE PYREXIAL CHILD

Among general measures in the treatment of the feverish child, none is more important than adequate rest, yet none is more difficult to secure, especially in serious illness in poor quality homes. Every experienced practitioner has seen a baby with pneumonia nursed on the knees of a relay of relatives and almost literally toasted in front of a fire. "Come into mummy's bed for a bit" may be appropriate for a child having a nightmare, and a bed in the living room may suit a child in the convalescent stage of rheumatic fever, but in an acute illness of any severity the child is best by himself in his own bed or cot. A warm room may be desirable, but it is better cool than too hot; cool moist air suits respiratory infections particularly well. A vest under the pyjama jacket and a jersey over the top "to guard against a chill" may encourage a mother to open a window and cool her child's sickroom. Sometimes a significant reduction of fever can be obtained by removing sources of artificial heat.

At the height of his illness, the sick child needs little stimulation from toys or entertainment. Left to himself he will drowse and sleep much of the day. As his condition improves and he begins to want his toys, convalescence begins, and it may be better to dress him and allow him to get up for an hour or two.

R. M. Mayon-White, The pyrexial child, *Practitioner*, March 1958, pp. 298-304

England

Of the great hospitals of England, two of the oldest and most widely known throughout the world are St. Bartholomew's and Guy's, both in London.

The tomb of Rahere.

St. Bartholomew's Hospital

St. Bartholomew's Hospital, together with the priory of St. Bartholomew the Great, was founded by Rahere, a royal minstrel, in 1123. While on a pilgrimage to Rome, Rahere became ill and, thinking he was about to die, he vowed that should he be allowed to return home, he would found a hospital for the poor. St. Bartholomew appeared to him in a vision and bade him found both hospital and church in Smithfield, then outside the walls of the City of London. Supported by the Bishop of London, Rahere approached the king, Henry I, who "graciously authorized him to carry out his proposals."

"The Good Samaritan," by William Hogarth, on the staircase leading to the Great Hall.

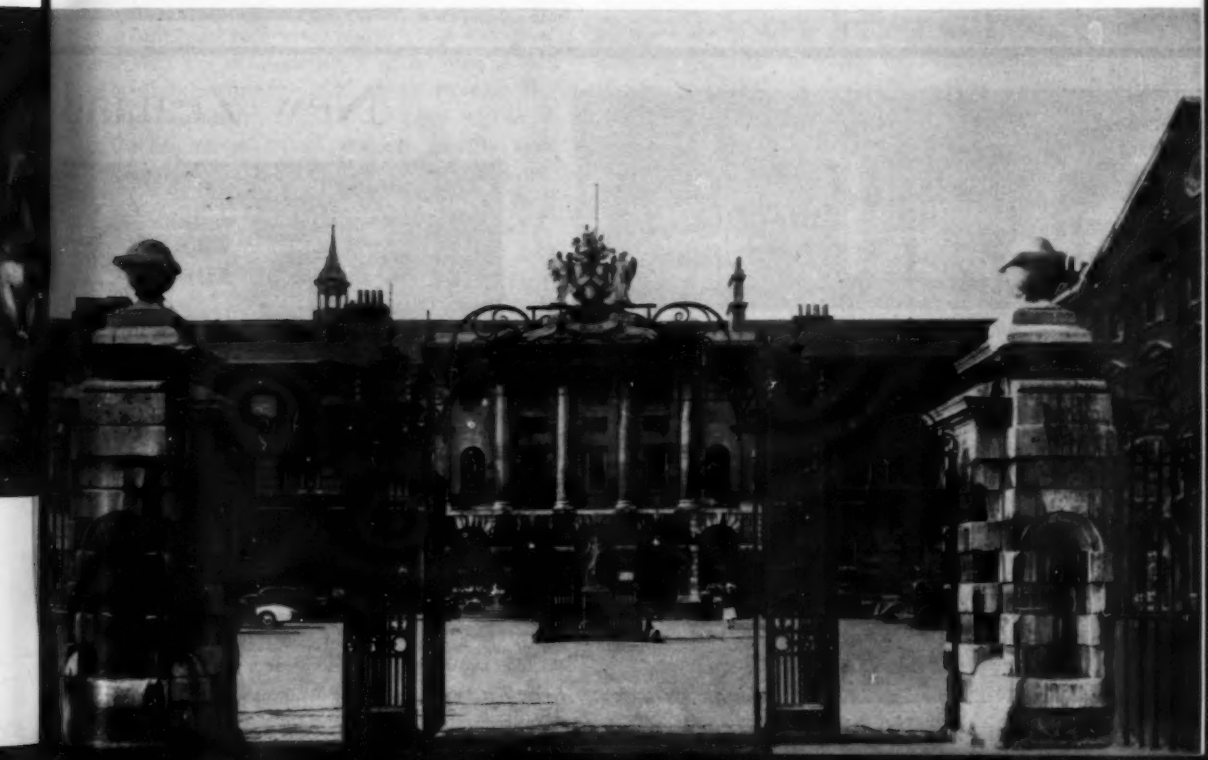
The Great Hall.

Guy's Hospital

Statue of Mr. Thomas Guy, founder of the hospital, which is in the front quadrangle.

Ground-floor view of the Gordon Museum showing three of the four rooms which are repeated above by two sets of galleries each. The cases in the center contain some of Towne's famous wax models of dissection which are approximately 150 years old.

Entrance to Guy's Hospital.



Scotland

Aerial view of The Royal Hospital for Sick Children, Glasgow.

Central building of Royal Infirmary of Edinburgh.

Gibraltar

The Colonial Hospital

New Zealand

Dunedin Public Hospital, Great King Street, opposite the Otago University Medical School.

Upper left. The new hospital at Wakari, also used for teaching and to house cancer research projects.

Lower left. Otago University Medical School buildings.

The Diagnostic Use of Radioactive Isotopes

3. DIAGNOSTIC RADIOISOTOPES IN HEMATOLOGY

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SECOND in importance to radioiodine is a series of radioisotopes that have been added to the diagnostic radioisotope laboratory to assist the hematologist. For the most part, these isotopes are directed at the erythrocyte, including its origin, development and life span; the main examples are radioiron, which enters the mammalian erythrocytic cycle in vivo only, and radiochromium, which can combine with the hemoglobin of intact cells in the test tube. Successful labeling of vitamin B_{12} with radiocobalt has added another means of evaluating megaloblastic anemia. Finally, estimation of whole-blood volume, as well as the volume of cells and plasma, is possible in a practical way only by radioisotopic means.

Volume of Plasma

The use of I^{131} is not limited to measurement of thyroidal function. Since iodine can be made to combine with most proteins, they can be labeled effectively with I^{131}. Among the many possible uses of this technic is evaluation of the volume of plasma using serum albumin labeled with I^{131} (often abbreviated to RISA, for radioiodinated serum albumin).

Volumes of plasma are measured conventionally by labeling the circulating plasmatic proteins with dyes such as Evans blue or Congo red. The degree of dilution of the injected dye is taken as a measure of the vascular space occupied by plasma. The use of RISA depends on the same principle. If a total dose of 200,000 cps of RISA is given intravenously and if five minutes later the radioactivity in the plasma is 100 cps per milliliter, the volume of the plasma is 200,000/100, or 2000 ml.

Because the measurement of radioactivity is simpler and at least as precise as measurement of the transmission of light, the RISA method very likely will continue to gain in acceptance.

Erythrocytic Volume

The hematologist is usually more concerned about the volume of erythrocytes than that of plasma. He can estimate the erythrocytic volume from the volume of plasma and of packed cells (hematocrit) using the following equations: (1) erythrocytic volume = whole-blood volume minus plasmatic volume and (2)

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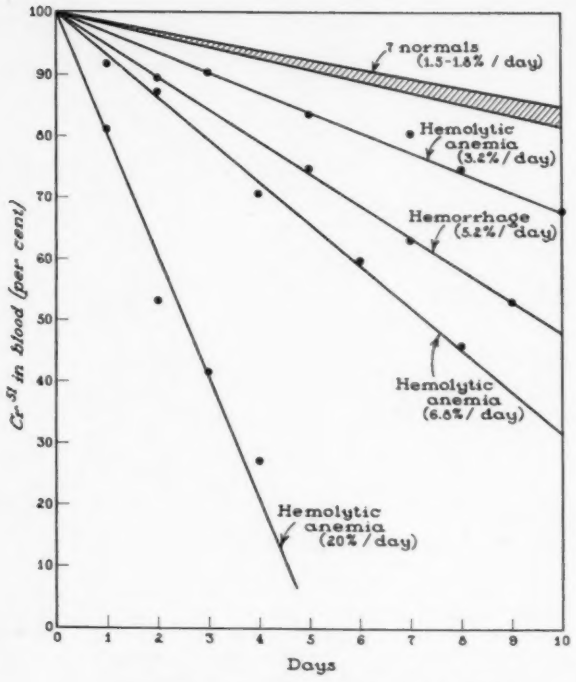

FIGURE 5. Disappearance of Cr^{51}-labeled erythrocytes from the circulation of three patients with hemolytic anemia and one with chronic intestinal tract bleeding. The disappearance rate in all cases is faster than normal, but there is no way to distinguish hemolytic disease from hemorrhagic disease on the basis of these curves alone.

(From Owen, Charles A., Jr.: Diagnostic Radioisotopes, 1958. Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.)

(Figures are numbered consecutively throughout the four parts of this article.)

whole-blood volume = plasmatic volume/(1.0 minus hematocrit) when the hematocrit value is expressed as a fraction of 1.0.

Unfortunately, values obtained on direct measurement of the erythrocytic volume usually are about 10 per cent less than the above calculations would suggest. This is presumed to be a reflection of the difference between the hematocrit value of blood in large vessels (such as the antecubital vein) and that in the capillaries.

No simple way exists to assess the erythrocytic volume directly; however, if the need arises, a radioisotopic method is available. When radioactive chromium (Cr^{51}), in the chemical form of chromate, is mixed with whole blood, most of the Cr^{51} enters the cells and is bound firmly to the hemoglobin molecules. After the cells are washed free of plasma and unbound Cr^{51}, they are suspended in an isotonic solution of sodium chloride and injected into the patient's blood stream. The calculation of the erythrocytic volume is the same as that for the plasmatic volume with RISA. What makes the procedure tedious is the time required for labeling and washing (one to two hours), as well as the need for the utmost precautions in order to maintain sterility.

Survival of Circulating Erythrocytes

Since erythrocytes can be labeled in vitro with Cr^{51}, which is a gamma-emitting isotope (making measurement simple) that has a half-life of almost a month, it is possible to follow the survival of these labeled erythrocytes in the patient. Another real advantage in the use of Cr^{51} is that the released Cr^{51} cannot relabel other erythrocytes. Only the oxidized (chromate) form can pass the erythrocytic wall; once in the cell, the chromium is reduced to the chromic state, remaining in this form during the remainder of its biologic life, which includes release from the erythrocyte, uptake by the reticuloendothelial system, and eventual excretion by the kidney.

The specimen of blood taken for labeling consists of a heterogeneous population of erythrocytes of all ages. Thus, the disappearance rate of Cr^{51} should be about 0.8 per cent per day on the basis of a normal cellular life of about 120 days in man. However, the Cr^{51} actually disappears at the rate of about 1.5 to 2 per cent per day in normal persons, because the chromium is not so firmly bound to the erythrocytes as one might wish; about 1 per cent "leaks" out of the cells each day. The observed disappearance rate is, therefore, the sum of degradation of erythrocytes plus leakage of Cr^{51}.

Once it is recognized that the normal disappearance of Cr^{51} from the blood stream is an unrealistic 2 per cent per day, patients who have hemolytic disease can be evaluated by comparison of the disappearance rates for Cr^{51}

(figure 5). My colleagues and I have observed patients with values ranging from less than 3 per cent per day to more than 50 per cent per day in whom the evidence was convincing that hemolytic disease was responsible.

It should be mentioned that one actually is measuring only the disappearance of Cr^{51}-labeled erythrocytes. If their accelerated disappearance is caused by bleeding, the result is the same as with a hemolytic process (figure 5). This precaution is particularly important in the case of underestimated or unsuspected bleeding into the alimentary tract. In fact, the appearance of Cr^{51} in the feces may be used as a measure of such bleeding.

Metabolism of Iron

While one aspect of the erythrocytic cycle can be measured directly and more simply with Cr^{51}, the availability of radioiron makes it possible to measure almost the entire cycle. Iron is absorbed from the upper part of the small intestine, probably in the ferrous form. This absorption requires a special mechanism of transport within the intestinal cells, and it is commonly believed that the ferritin transport system varies with the level of iron stores in the body. The more depleted the stores become, the more active is the intestinal absorption of iron.

Once absorbed, the iron becomes bound to a specific "iron-binding" protein located with the beta globulins of plasma. The iron is now available to the marrow for incorporation into new erythrocytes, to the various tissues that synthesize iron-containing enzymes, and to the depots of iron. Under normal circumstances, most of the plasmatic iron is directed toward the erythropoietic tissue. This is understandable when it is recognized that 1/120 of a person's blood is being destroyed daily and, therefore, synthesized daily in order to keep the balance. In a person who has a blood volume of 5 l., this amounts to a daily loss of about 40 ml. of blood, or about 20 ml. of erythrocytes. This amount of blood contains about 20 mg. of iron. Since the normal concentration of plasmatic iron is about 1 μg. per milliliter, all the iron of the entire volume of plasma must be deposited in the erythropoietic tissue 5 to 10 times each day to keep pace.

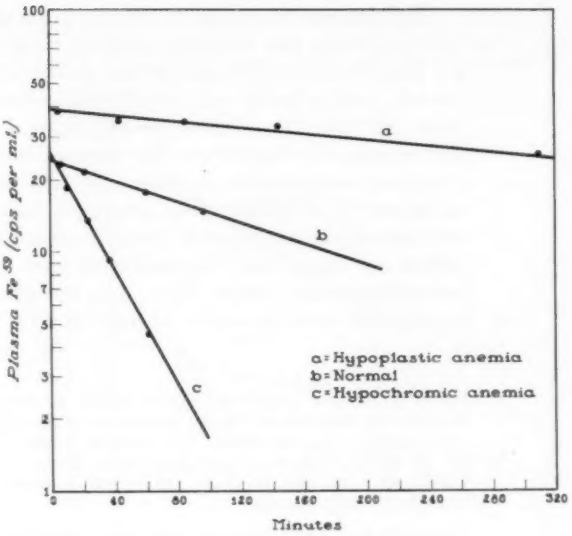

FIGURE 6. Rates of disappearance of Fe^{59} after the intravenous injection of ferrous[59] citrate. The patient with poorly functioning marrow (hypoplastic anemia) removed the Fe^{59} from the blood extremely slowly, and the patient who had iron deficiency hypochromic anemia cleared it extremely rapidly.

(From Owen, Charles A., Jr.: Diagnostic Radioisotopes, 1958. Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.)

Radioiron (Fe^{59}), which is a beta- and gamma-emitting isotope with a half-life of one and one-half months, can be inserted into the erythron's cycle to trace the efficiency of iron metabolism.

Plasma turnover of iron—When a solution of a salt of Fe^{59} is given intravenously, the Fe^{59} disappears from the plasma at a steady rate that apparently depends on the concentration of plasmatic iron and the avidity of the tissues for iron (figure 6). If the concentration of stable iron is measured, simple arithmetic computation leads to an expression of the amount of iron leaving the blood stream per unit of time, or the "plasma iron turnover." Such a procedure requires about three hours of the patient's time. Some observers have questioned the validity of the calculation of turnover of iron in the plasma, for the concentration of iron tends to vary widely during its diurnal cycle.

This turnover of iron in the plasma is about 0.3 to 0.4 mg. per kilogram of body weight per day. It may be increased in iron deficiency anemia, polycythemia vera and hemochromatosis. The first two of these conditions represent increased erythropoiesis, the former being a normal compensatory reaction, the latter a malignant hyperactivity. The increased turnover rate of plasmatic iron in hemochromatosis reflects an exaggerated deposition of iron in nonerythropoietic tissue. Thus, it is not safe to conclude from the values of plasmatic Fe^{59} and stable iron alone that the marrow is overactive.

FIGURE 7. Selective uptake and release of Fe^{59} by bone marrow as a mirror image of the appearance of labeled erythrocytes in the circulation. The apparent uptake of Fe^{59} by the liver and spleen probably reflects rib-marrow uptake, since activity in these organs was measured through the lower rib cage.

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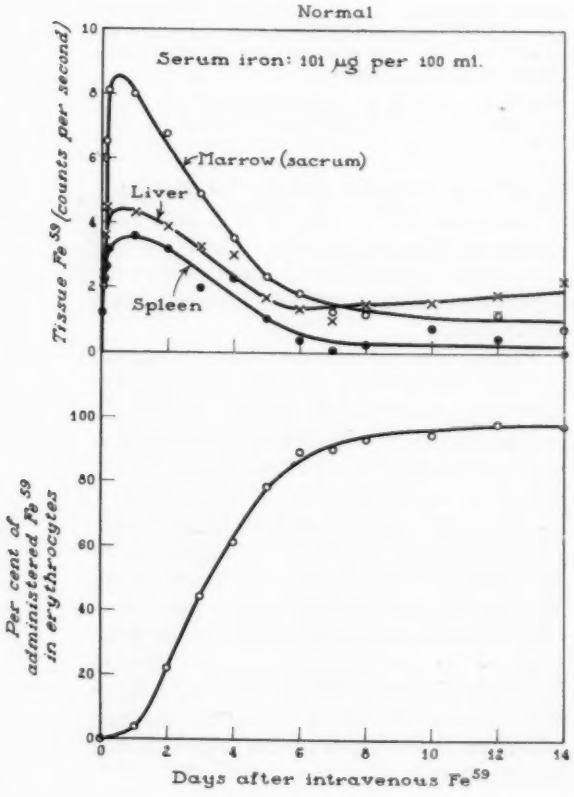

Tissue localization of Fe^{59}—If, in addition to assays of plasma, counters are directed at various regions of the patient's body, it is usually possible to evaluate the organ to which Fe^{59} is attracted primarily. For these measurements, the liver (lower right rib cage), spleen (lower left rib cage), and bone marrow (either the sacrum or the upper thoracic vertebrae above the level of the liver and spleen) are selected. In normal persons, the uptake of Fe^{59} by the marrow quickly outdoes that by the liver and spleen (figure 7). This evaluation may be made during the three hour period required to establish the disappearance rate of Fe^{59} from plasma.

Turnover rate of erythrocytic iron—If Fe^{59} is selectively localized in the marrow, one reasonably may assume that the iron will be utilized for the synthesis of erythrocytes. Of course, it also may be used erythropoietically by the spleen or liver in instances of myeloid metaplasia.

To be certain of the final disposition of the Fe^{59} requires continued study of the patient for at least a week. Within 7 to 10 days, the normal adult will have transferred 80 to 90 per cent of the original dose of Fe^{59} into circulating erythrocytes. The conventional expression of "iron turnover" involves multiplying the turnover of plasmatic iron (milligrams per kilogram of body weight per day) by the percentage eventually returned to the circulation in erythrocytes. The normal range is about 0.25 mg. per kilogram per day.

By following the appearance of radioactive erythrocytes, one can determine precisely whether or not the assumptions based on the original organ localizations are valid. Thus, Fe^{59}-labeled erythrocytes do appear in splenic myeloid metaplasia (figure 8). In hemochromatosis or certain instances of hemolytic anemia, the Fe^{59} deposited in the liver does not appear to any important extent in the circulation. On the other hand, active uptake by the marrow of plasmatic Fe^{59} does not guarantee efficient erythropoiesis; pernicious anemia in relapse is an example.

Survival of Fe^{59}-labeled erythrocytes—If

time is not a limitation, the patient may be studied for a number of weeks to estimate the survival of erythrocytes. Since a uniform population of new erythrocytes only is labeled with the Fe^{59}, all the labeled cells should survive the full life span. This is different from the findings when erythrocytes are labeled with Cr^{51}; in the latter instance, cells of all ages (0 to 120 days) are labeled equally, and thus they start disappearing immediately as the oldest cells disintegrate.

Actual experience shows that normal erythrocytes labeled with Fe^{59} do not all survive the anticipated 120 days. Rather, the erythrocytic radioactivity is constant for about 80 or 90 days (if one makes a correction for the physical decay of the Fe^{59}), after which the curve begins to fall. Since the iron is reutilized, a sharp drop never occurs; instead, an S-shaped drop is present between the eightieth and 160th days, with the midpoint at about the 120th day, which represents the average life span of normal adult human erythrocytes.

In patients who have hemolytic disease or hemorrhagic loss of the labeled erythrocytes, the radioactivity of the blood does not remain constant but shows a decrease reflecting the degree of hemolysis or bleeding.

Simultaneous use of Fe^{59} and Cr^{51}—Evaluation of erythrocytic survival by use of Fe^{59} cannot commence until the erythrocytes in the blood stream are maximally labeled, which usually is 7 to 10 days after administration of the iron. However, with the newer technics of counting radioactivity, one may follow erythrocyte-Fe^{59} synthesis and erythrocyte-Cr^{51} survival simultaneously. This permits a more or less nearly complete evaluation of the entire erythrocytic cycle within a period of about two weeks.

The ability to measure these two isotopes simultaneously depends on the difference between the gamma rays of Fe^{59} and those of Cr^{51}. The latter are weaker and therefore they may be discriminated against by interposing appropriate lead or electronic filters between the mixture and the radiation detector.

Absorption of iron—The only phase of the metabolic cycle of iron that cannot be tested simply is intestinal absorption. Current methods involve the feeding of several milligrams of a salt of iron labeled with a radioisotope of iron. The normal person absorbs only about 5 per cent of such doses, so that reduced absorption cannot be measured.

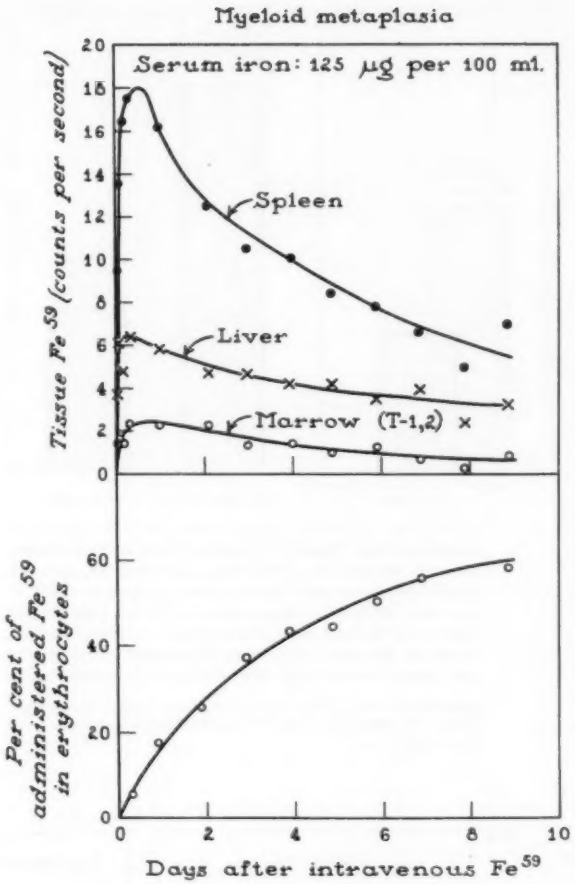
Myeloid metaplasia
Serum iron: 125 μg per 100 ml.
Tissue Fe 59 (counts per second)
Spleen
Liver
Marrow (T-1,2) ×
Per cent of administered Fe 59 in erythrocytes
Days after intravenous Fe59

FIGURE 8. Selective uptake of Fe^{59} by the spleen in a patient with myeloid metaplasia. The appearance of labeled erythrocytes indicates that the splenic erythropoietic tissue is functioning adequately. The marrow is seen to be almost inactive.

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Absorption of Vitamin B_{12} Labeled With Radioactive Cobalt

Certain microorganisms synthesize vitamin B_{12} during the normal course of their metabo-

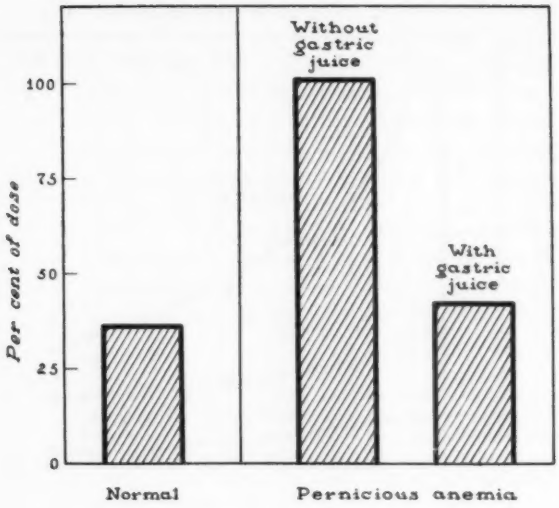

FIGURE 9. The Heinle (fecal excretion) test of absorption of vitamin B_{12}. The radioactive vitamin was absorbed by the normal person (fecal excretion about 35 per cent of the oral dose) but not by the patient with pernicious anemia (100 per cent fecal excretion) until a source of intrinsic factor (normal human gastric juice) was administered along with the labeled vitamin.

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lism. The synthesis includes the incorporation of an atom of cobalt into each molecule of the vitamin. If one were to culture *Streptomyces*, for example, on a medium containing radioactive cobalt, a certain number of molecules of labeled vitamin would be produced. Several radioisotopes of cobalt are known (Co^{56}, Co^{57}, Co^{58}, Co^{60}) but until recently only vitamin B_{12} incorporating Co^{60} has been commercially available. This is unfortunate, since Co^{60} has a half-life of about five years, which necessitates the use of minute doses in man; the other isotopes have half-lives measured in months.

The availability of radioactive vitamin B_{12} makes it possible to measure intestinal absorption of this vitamin, which is of particular importance in the early diagnosis of pernicious anemia. Several methods have been proposed. The Heinle test depends on quantitation of the fecal excretion of the labeled vitamin; the fraction of the dose that is not excreted is assumed to be absorbed (figure 9). The Glass test depends on hepatic localization of the vitamin (figure 10). If vitamin B_{12} is absorbed, radioactivity is demonstrable when a counter is directed toward the liver; the lack of radioactivity suggests that intestinal absorption is inadequate.

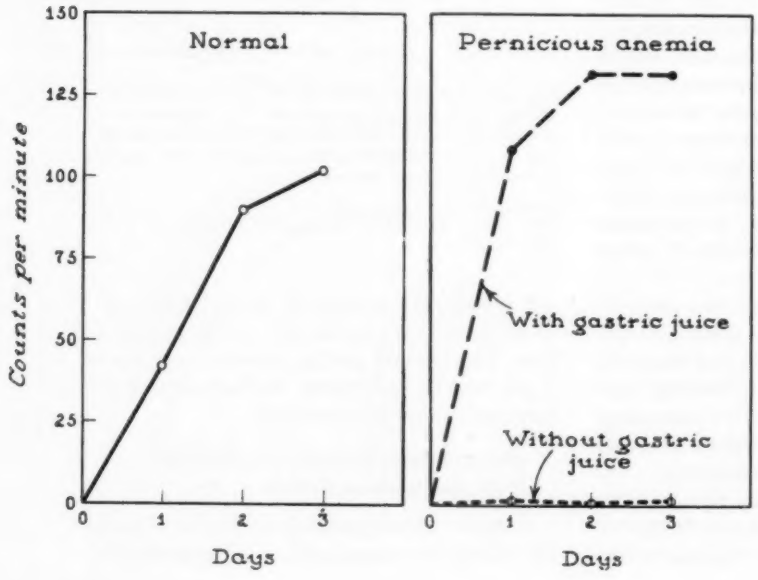

FIGURE 10. The Glass (hepatic uptake) test of absorption of vitamin B_{12}. The radioactivity is measured over the liver and over the lower part of the abdomen (fecal Co^{60}) for several days after an oral dose of labeled vitamin B_{12}. The difference between the paired readings is assumed to be hepatic uptake of the vitamin. No uptake was evident in the patient with pernicious anemia until gastric juice was added.

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The most widely used test for measuring absorption of vitamin B_{12}, the Schilling test, depends on forced urinary excretion of freshly absorbed vitamin (figure 11). The excretion is induced by injection of a large dose (1 mg.) of nonradioactive vitamin B_{12} about two hours after oral administration of the labeled vitamin. In the presence of adequate renal function, about one-third of the absorbed radiovitamin appears in the urine within a period of 18 to 24 hours.

According to the tenets of Castle, absence of intestinal intrinsic factor prevents absorption of vitamin B_{12}. Use of radioactive vitamin B_{12} can assess the lack of absorption precisely. A variety of intestinal abnormalities, however, including sprue and diverticulosis, also can retard absorption of this vitamin. At the Mayo Clinic, my colleagues and I routinely carry out a second step if results of the first part of the absorption test are abnormal. The labeled vitamin is given along with a commercial preparation of intrinsic factor; malabsorption should be corrected if the disease is addisonian pernicious anemia, but it is not corrected in the presence of intestinal disease. Examples of results with the Schilling test are shown in the accompanying table.

URINARY EXCRETION OF VITAMIN B_{12} LABELED WITH Co^{60}

	WITHOUT ADDED INTRINSIC FACTOR	WITH ADDED INTRINSIC FACTOR
Normal	> 8 per cent of dose	
Pernicious anemia	0 to 3 per cent	> 8 per cent
Sprue	< 8 per cent*	No improvement
Diverticulosis	< 8 per cent*	No improvement†

*Varies with the severity of the disease.

†Tends to become normal after administration of tetracycline.

The need for measurement of the activity of intrinsic factor is increasingly important since vitamin B_{12} is so commonly taken by patients with anemia of any type. The tests utilizing radioactivity are equally effective whether or not a patient is receiving therapeutic doses of vitamin B_{12}, and whether or not anemia exists.

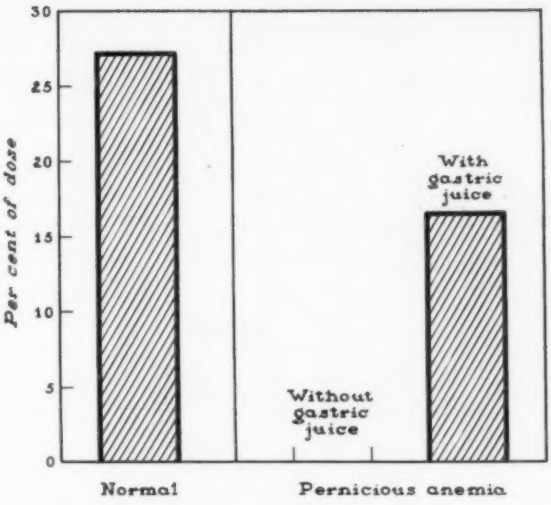

FIGURE 11. The Schilling (urinary excretion) test of absorption of vitamin B_{12}. Two hours after an oral dose of radioactive vitamin B_{12}, the patient is given an injection of 1 mg. of nonradioactive vitamin B_{12}. A portion of the intestinally absorbed vitamin is thus "flushed" through the kidneys if any absorption has occurred. This did not take place in the patient with pernicious anemia until a source of intrinsic factor was added.

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Comment and Conclusions

Whole-blood, plasmatic and erythrocytic volumes can be quantitated by isotopic means beyond the capacity of the dye methods, which are limited to plasmatic volumes alone.

The availability of two radioisotopes that can label erythrocytes, namely, Cr^{51} in vitro and Fe^{59} in vivo, renders possible the measurement of most of the erythrocytic life cycle.

Activity of intrinsic factor in patients suspected of having pernicious anemia, whether anemic or not, can be evaluated with vitamin B_{12} labeled with Co^{60}.

If the early tentative labeling technics of leukocytes and platelets become established, the hematologist may find the radioisotope laboratory a most important ally in the evaluation of diagnostically difficult patients.

Part 4, "Newer diagnostic procedures using radioisotopes," will be published next month.

Nutrition in Clinical Medicine

POSTGRADUATE MEDICINE this month starts a new series of discussions in the field of nutrition as it relates to health and disease in order to focus attention on the general role of diet in the maintenance of health and on the place of nutrition in clinical medicine.

JEAN MAYER

Conducting this new department will be Dr. Jean Mayer, Associate Professor of Nutrition at the Harvard School of Public Health. On the following pages, Dr. Mayer inaugurates the series and outlines its aims. His articles on the subject will later be supplemented by discussions on specific topics by guest contributors.

Born in Paris, France, in 1920, Dr. Mayer there received the B. Litt., B.Sc. and M.Sc. degrees with high honors. In 1948 he was granted the Ph.D. degree from Yale, and in 1950 he completed work for the D.Sc. degree, "with highest honors," at the Sorbonne in Paris.

After fellowships at the Ecole Normale Supérieure in Paris in 1939 and at Yale from 1946 to 1948, he was research associate in pharmacology at George Washington University Medical School. During this period he was a member of the Nutrition Division of the Food and Agriculture Organization of the UN. He became a member of the faculty at Harvard in 1950.

During World War II, Dr. Mayer served for five years as a field artillery officer, first in the French army and then with the Free French forces. His military honors include the *Croix de guerre* with palm and stars and the Resistance Medal.

Dr. Mayer is a member of many professional organizations and has several times served on technical committees of the Food and Agriculture Organization and World Health Organization.

Readers are invited to send questions relating to nutrition to the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

Nutrition

JEAN MAYER*

Harvard University School of Public Health, Boston

It has become a truism in medical education that the physician must learn to treat the whole patient and not just the disease. This is never any truer than where diet is concerned. If it is to succeed, any nutritional program or dietary regimen must take into account the patient's financial status, his level of education, in some instances his religious practices, the familial background of food preparation, and, of course, the local availability of foodstuffs. The casual advice, "Better cut down on calories," or "Cut down on fats," or "Keep the proteins up" may be unintelligible to the patient or may entail such difficulties that he is unable to heed it without help. Even the technic of assessing the nutritional intake of a cooperative patient is fraught with difficulties involving economics, food analysis, cooking practices, etc. Yet, as the immediate threat of infectious diseases recedes as one of the main causes of death and as Americans are increasingly felled by degenerative diseases, cardiovascular, renal and hepatic syndromes, diabetes, and malignancies often aggravated in frequency and in severity by obesity, the metabolic and nutritional factors loom larger in the thinking of practicing physicians.

It is the aim of this series to bring to the readers of POSTGRADUATE MEDICINE not only new clinically important nutritional facts as they are discovered but also a summary of the trend in nutritional research as it applies to clinical medicine, and something of the present thinking of nutritionists.

Early History

In nutrition, as in other fields, the present is the child of the past. It may be useful at the outset of this series to remind the reader of the general lines of the evolution which has made the science of nutrition what it is today. Very broadly this evolution can be divided into four periods: (1) the prescientific period, extending from the dim beginnings of the Stone Age to the second half of the eighteenth century, following Lavoisier's introduction of the calorimetric concepts and measurements; (2) the age of study of caloric and nitrogen balance, the nineteenth century; (3) the era of the discovery of trace elements, vitamins and essential amino acids and the era of deficiency diseases, extending from Hopkins to the 1940s; and (4) since the end of World War II, the

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development of the study of the role of nutrition in degenerative diseases and the recognition of the fact that what is in the diet can be almost as important as what is missing from the diet.

An instinctive knowledge of food is necessary for survival. In a long series of trials and errors—sometimes mortal errors—the number of animals and plants which can provide food has been extended. The idea that food does more than assuage hunger is very old. Certain beliefs, such as the idea that consumption of the heart or flesh of brave or strong animals would confer the same virtues to the warriors of the tribe, appeared with the dawn of human history. Food taboos also appeared during the Stone Age. While some of these taboos may well have had something to do with the wholesomeness of certain foods (e.g., the Biblical prohibition of pork may have been based on the recognition of frequent infestation of swine with *Trichinella*), most of these edicts seem to have had no basis in fact. Examples of such practices were the Egyptian prohibition of beef or chicken for kings and the Biblical edict against hare.

Closely allied with the problem of taboos and superstitious beliefs was the search for foodstuffs which also would be remedies. Many herbs and parts of plants or animals were prescribed because of their shape, their color or some other property unrelated to any demonstrable pharmacologic effect. But the recommendations of the "Ebers Papyrus" (1600 B.C.), of Hippocrates (fifth century B.C.), of medieval writers who advocated liver for eye diseases and night blindness, and of Cartier's Indians, who used evergreen needle infusions for scurvy are early examples of prescriptions for deficiency diseases. Incidentally, Hippocrates, the founder of scientific medicine, paid considerable attention to nutrition in his writings. Many of his opinions are difficult to justify; for example, his belief that beef is more difficult to digest than pork, or that fish should be roasted rather than boiled for feverish patients. But this abhorrence both of extreme abstemiousness and diet restriction and of excessive intake without corresponding physical labor is still good nutritional advice.

Lavoisier's Investigations

Probably the greatest turning point in the history of biology and of medicine was the investigation of combustion conducted by Lavoisier (1743 to 1794). In addition to introducing measurements in biologic and chemical studies, Lavoisier in these experiments laid the basis for our understanding of caloric expenditures and requirements. The summary of the experiments conducted on his collaborator Seguin in 1785 illustrates well the modern outlook of this great innovator: Of every 100 parts oxygen Seguin absorbed in respiration, only 81 parts reappeared as carbonic acid gas, the remaining 19 parts being combined with hydrogen to form water. He absorbed the lowest amount of oxygen when in a state of rest at a comfortable temperature after an overnight fast (now called basal metabolism). When fasting, Seguin absorbed a greater amount of oxygen at a temperature of 12° C. than at 26° C. (effect of cold on stimulating oxidations). When he took food but remained at rest, he absorbed more oxygen than when he had had no food (specific dynamic action). The greatest increase in oxygen absorption (up to 200 or 300 per cent) came from doing mechanical work. Nevertheless, even 170 years after Lavoisier's experiments, the increase in caloric expenditure due to exercise is still too often belittled when reducing regimens are prescribed.

Nineteenth-century Developments

The results of Lavoisier's work were extended by the work of the nineteenth-century physiologists and chemists. Vauquelin, Magendie, Prout, Mulder and, especially, Von Liebig (1803 to 1873) developed concepts and methods of analyses permitting the establishment of food composition tables. These are still the essential tool of the nutritionist, since any reassessment of the value of a diet and any dietary recommendations eventually must be translated in terms of foods in order to be of practical use.

Boussingault (1802 to 1887) studied absorption and digestion of foodstuffs. The proportion of carbohydrate, protein and fat and

their contribution to the caloric content of foodstuffs became the basis of nutrition, with only scant attention being given to the minerals and almost none to the other nutritional factors.

Atwater, who returned to this country in 1892 following a period of European study, tried to put all of practical nutrition on the basis of cost of calories and protein. In effect, he advocated deriving the diet from cereals, peas and beans, and omitting fruits and garden vegetables. Both Von Voit and Atwater recommended large amounts of protein for adults (approximately 150 gm. per day), in spite of Chittenden's experiments showing that men could live and work with less than one-third this amount of protein intake.

Essential Nutrients

Another great turning point came at the beginning of this century when the concepts of essential nutrients came into existence. This was tantamount to recognizing that while the organism is a good chemist, it is not perfect; while it can synthesize thousands of complicated molecules, there are a number of structures—vitamins and essential amino and fatty acids—which it cannot synthesize. Hopkins showed that tryptophan was such an indispensable nutrient. Osborn and Mendel showed that the addition of tryptophan and lysine considerably improved the biologic value of corn proteins; the chief corn protein zein is particularly low in these amino acids. Systematically using semisynthetic experimental diets, McCollum and Davis showed that the minimum adequate diet for the rat must provide, in addition to the long-known nutrients, two unidentified factors which they called "fat-soluble A" and "water-soluble B."

It is remarkable that while clinicians—Linde, Trousseau and Eijkman—first implicated nutrition in diseases such as scurvy, rickets and beriberi, it is to chemists—Hopkins, Mendel, McCollum and others—that we owe the concept of deficiency diseases as clinical entities. It seems almost incredible that barely a century ago Charles Caldwell, one of the most prominent clinicians of his time, was writing a 95 page pamphlet to denounce Von Liebig and proclaim that chemistry had nothing to contribute to medical science!

Later Advances

It is unnecessary to point out the extreme speed at which our understanding of the deficiency diseases, the characterization and synthesis of vitamins, and the translation of experimental nutrition into clinical advancement have progressed between World War I and World War II. The pasteurian revolution is the only comparable explosion of knowledge in the history of medicine.

Rickets, once the most prevalent disease condition in Western cities, was almost wiped out in 10 years by the widespread use of fish-liver oils and by the fortification of milk with vitamin D. Goiter was eliminated from entire populations by the addition of iodine to salt. Flour enrichment and diet improvement have so effectively dealt with pellagra that it has been impossible for several years to locate a pellagrous patient in the whole state of Georgia to demonstrate the once common signs of the disease to the students of the Medical College of Georgia.

At the same time that our experimental and clinical knowledge improved, our sense of social responsibility increased. It was believed that educated nations could not tolerate the fact that diseases which could be easily prevented should continue to kill and disable millions of human beings. In his famous book, "Diet, Health and Income," John Boyd Orr showed that in Scotland poor growth and morbidity were much more prevalent among the poor classes than among the wealthy. Hazel Stiebeling in this country and André Mayer in France conducted nutritional surveys which demonstrated that many children and adults, particularly in the poorer classes, were undernourished or malnourished.

In the 1930s the League of Nations called together a committee of physiologists which promulgated the first set of recommended dietary allowances as well as a practical handbook on the assessment of the nutritional status of populations. This impetus was further accelerated by the preoccupation with food problems during World War II. Scientific advisory

bodies, such as the United States National Research Council Food and Nutrition Board, came into existence on several continents. More important, over 60 nations combined their efforts to improve nutrition all over the world. The Food and Agriculture Organization of the United Nations, the Nutrition Section of the World Health Organization, and the United Nations International Children's Emergency Fund were some of the offspring of this great movement. In many regions the emergency measures taken by some of the "crisis committees" created by FAO averted the widespread starvation which otherwise would have followed the end of the war. UNICEF has started and encouraged child-feeding programs covering millions of children in Asia, Africa and Latin America. FAO and WHO have initiated, supported and publicized epidemiologic and clinical studies of kwashiorkor, the most widespread deficiency syndrome found in poor areas, which apparently is due to lack of good-quality proteins in the diet during early childhood following weaning.

Diet and Degenerative Disease

The renewed interest in *undernutrition* during World War II resulted directly in an interest in *overnutrition*. Observers were struck by the drastic decrease in the number of patients hospitalized with cardiovascular conditions during the famine accompanying the siege of Leningrad. When the siege was broken and the famine relieved, the "refeeding" period was accompanied by an upsurge in cardiovascular conditions. Statistics accumulated by life insurance companies emphasized the positive correlation of excess weight and mortality not only from cardiovascular diseases but also from liver conditions, diabetes, increased operative risk, etc. This in turn stimulated interest in the etiology and pathogenesis of obesity and in its associative and causative links to disease.

Considerable interest also was generated by Keys' suggestion that the presence of a high proportion of fat in the diet was associated with hypercholesteremia, atherosclerosis and coronary disease. A lively and constructive experimental controversy still rages as to the relative influence on cholesterol levels of the proportion of animal and vegetable fats, degree of saturation of the fat, concentration of polyunsaturated (essential) fatty acids, presence of plant sterols, etc.

Long-term Studies

Another recent development has been the recognition that the time factor should be accorded more attention in nutrition. For example, Best showed in experimental animals that choline deficiency during growth may result in renal hypertension in old age; many investigators have produced congenital malformations by feeding to pregnant animals deficient diets at certain crucial periods during pregnancy. The links between diet and degenerative diseases also point to the need for longer-term studies.

This introduction of longer duration in nutritional problems re-emphasized the fact, known by experienced physicians since Hippocrates, that to understand how a given disease affects a given patient one must consider not only the disease agent but also the patient's individual constitution. Recent trends emphasize the importance of studying the interaction of constitutional and nutritional factors. For example, it is becoming clear that there are strong genetic determinants in the ability of an organism to switch from a high carbohydrate to a high fat diet without accumulating excessive adiposity. It is also apparent that there are constitutional differences in the ability to regulate food intake at low exercise levels; in other words, the appetite of certain individuals is reduced proportionately when their activity is reduced to low levels; others are constitutionally prone to overeat if their activity is too low.

Recognition of Other Nutritional Problems

There are many other nutritional problems which are receiving renewed attention, such as the relationship of diet to aging, to physical and intellectual performance, and to reproduction and the special nutritional problems of adolescence, arising in part from the recogni-

tion of the widespread character of iron deficiency anemia in this age group. Parenteral nutrition, especially when prolonged, urgently raises the whole problem of nutritional requirements. Advances in general nutrition have led to a critical re-examination of many of the classic special diets. Is the high fat ulcer diet dangerous from the viewpoint of atherosclerosis? Is the rice diet deficient in protein? What of electrolyte balance in the low salt diet? The problem of food additives, of contamination with insecticides, is one which should raise more serious toxicologic consideration than it has in the past.

Study of the mode of action of antimetabolites (a general class of substances which comprise many of the antibiotics) has focused attention on the problem of "differential" nutrition, balancing the requirements of the host (patient) against those of the parasites. There are indications that the understanding of the mode of action of viruses and of malignant cells may involve similar problems.

The development of cultural anthropology also has placed renewed emphasis on what may be called the non-nutritional aspects of foods. Certain food practices and certain dishes may have a symbolic significance which rejoins through conscious and subconscious associations the taboos of an earlier age as well as buried childhood memories. Realization of these overtones may be of considerable importance to the psychiatrist or to the general practitioner trying to re-educate his patient to better nutrition.

The relationship of alcoholism to nutritional factors is also of great importance in our society. The addiction of many patients to fad diets, "nature foods," etc. causes an unnecessary drain on their budgets, often results in an unbalanced diet, and may be a symptom of more serious psychologic difficulties which can be understood only in terms of their general emotional background.

Summary

It can be seen that, far from coming to a dead end with the solving of the classic deficiencies, the scope of the science of nutrition has expanded considerably in the past few years. The nutritional aspect should be considered in the treatment of any patient, not just the pediatric, obstetric or postoperative patient. In many ways nutrition is the single most important aspect of the environment of a patient. It is our hope that this series will help practitioners to translate new nutritional knowledge into the daily care of their patients.

POSTGRADUATE MEDICAL DEBATE

Treatment of Rheumatoid Arthritis

Salicylates

ROBERT C. BATTERMAN*

New York Medical College and Metropolitan Medical Center, New York

Corticosteroids

PAUL O. HAGEMANN

St. Louis

Statement by Dr. Batterman:

ARTHRITIC complaints have been treated by salicylate-containing preparations for many centuries. In 1860 with synthesis of the pure chemical, the first major advance in arthritis therapy was noted. Shortly thereafter sodium salicylate was accepted as an effective and safe antirheumatic and analgesic medication. The antirheumatic effects of acetylsalicylic acid were a chance discovery about the turn of the century, and since then any discussion of salicylate therapy has considered the effects of sodium salicylate and aspirin as one. Other salicylate derivatives, such as salicylamide, in my experience are not as effective as sodium salicylate or aspirin, and therefore will not be considered in this review.

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ROBERT C. BATTERMAN

The mechanism and site of the antirheumatic and anti-inflammatory effects of the salicylates are wholly unknown. With the advent of cortisone and ACTH, the possibility arose that salicylates mediate their effects through stimulation of pituitary-adrenal systems. However, after eight years of intensive investigation, evidence disproving this hypothesis has finally cumulated to convince almost everyone.

At best, in spite of an unquestionable anti-inflammatory effect, salicylates are only palliative or symptomatic medications. As compared with steroid therapy, there is no essential dif-

ference in effect other than degree. The original hopes for cortisone and the far more recent derivatives have not been realized. Although these compounds possess a profound anti-inflammatory and antirheumatic action, they are not specific medications for the rheumatoid process or any other arthritic condition but are only suppressive symptomatic agents. It is in this regard that any therapy for arthritis should be considered. If a specific action cannot be attained, then that medication is primarily symptomatic and should be used with full consideration of the principles demanded of symptomatic medications. These principles have been entirely neglected for all steroid compounds in past or current use. With few exceptions, arthritis and related conditions are chronic disorders. A fundamental principle requires that medications recommended for chronic use should have little if any propensity for development of tolerance, cumulative toxic manifestations, and addiction. Analysis of the results achieved with chronic administration of cortisone, hydrocortisone and, to a lesser degree, with prednisone and prednisolone is not conducive to unqualified recommendation of these preparations for the usually encountered patient with a musculoskeletal complaint.

It is too soon to state whether the newer steroids will be free of the complications observed in the forementioned. Only the most serious effects of chronic administration of these preparations will be noted. Each untoward reaction has been well recognized, so that detailed discussion is not required. The following complications have occurred with their use: (1) aggravation or development of permanent diabetes mellitus; (2) elevation of blood pressure and development of sustained hypertension; (3) toxic psychosis; (4) generalized osteoporosis related to a negative calcium balance and resultant spontaneous fractures of vertebrae, hips or other stress areas; (5) absorption of skeletal areas such as neck of femur with telescoping of affected parts and resultant shortening and mechanical problems of weight bearing and walking; (6) aggravation of peptic ulcer with increased pain, hemorrhage or perforation (an acute condition in the abdomen may exist without any sign or symptom suggestive of peritonitis or inflammatory response); (7) impairment of wound healing; (8) development of thrombocytopenic purpura; (9) decreased clotting and prothrombin time with occurrence of thromboembolic phenomena in peripheral vessels and heart; (10) development of collagen diseases such as periarteritis and an increased finding of lupus erythematosus cells on blood and bone marrow examinations; (11) severe electrolyte imbalance, shocklike state and abstinence phenomena suggestive of addiction which might result from abrupt withdrawal of use; and (12) when surgery is required for patients who have had previous steroid therapy, they must be treated preoperatively with steroids to avoid acute stresslike shock secondary to adrenal insufficiency.

Although these toxic manifestations are serious in their own right, one might make allowances for their occurrence if the dread crippling and progressive rheumatoid state were controlled or cured. This does not occur. Not only will the rheumatoid disease continue unabated to the full development of joint destruction and deformity, in spite of symptomatic relief, but the patient also will experience a decreasing relief because of tolerance. The partial control or suppression of the arthritis has been labeled "arthritis in miniature" with the thought that partial control is better than no control. This is a poor subterfuge for ineffectual therapy.

Symptomatic relief with sodium salicylate or aspirin may not be dramatic, but when evident it is very satisfactory, and is attained in the majority of cases with assurance, without development of tolerance, and with few manifestations of nonserious cumulative toxicity.

The disadvantages of salicylate therapy, regardless of preparation, revolve about two major aspects. The predictability of satisfactory analgesia is no greater than 60 per cent. This effect is achieved within two or three days of repeated drug administration, usually at four hour intervals, and cannot be attained faster by larger doses or parenteral use. Relief depends entirely on the duration of salicylate present within the body. At night or the first

thing in the morning, all pain recurs, regardless of the completeness of analgesia during the daytime, because of the elimination of the drug during the night hours. Readministration of salicylates on arising again restores complete analgesia. This seesawing effect accounts for patients insisting that salicylates are not effective, whereas complete relief may be attained as long as the medication is taken at four hour intervals.

The second aspect is related to cumulative gastric intolerance for both aspirin and sodium salicylate. A single 0.3 or 0.6 gm. dose of either preparation is of no consequence. Tests with repeated doses of the same magnitude indicate that at the end of one week the incidence of gastric intolerance is still low and similar for both preparations at the 0.3 gm. level, but with 0.6 gm. every four hours, sodium salicylate is more irritating than aspirin. Since gastrointestinal disturbances are found more frequently in arthritic patients than in the general population, the problem of prolonged therapy with a well-tolerated salicylate is still a major challenge. Simultaneous administration of alkalies or buffers with salicylate is of no value in decreasing gastric intolerance.

Aspirin differs from sodium salicylate in that very rarely a patient may manifest a true allergy to aspirin. This is not the usual gastrointestinal intolerance, which is seldom a true allergic manifestation, but rather urticaria, angioneurotic edema or bronchial asthma. Patients allergic to aspirin can tolerate sodium salicylate without any difficulty. Skin rashes and pruritus occur with both medications, are not serious, and subside promptly with discontinuation of therapy.

High doses of either salicylate serve no useful purpose. The usual dose of 0.6 gm. every four hours is as effective without occurrence of salicylism. None of the cumulative toxic manifestations noted for steroid therapy occur with salicylates.

Steroid therapy is useful in certain musculoskeletal conditions requiring short-term intensive therapy, in conjunction with active rehabilitation and physical therapy. Long-term or chronic use of steroids requires careful observation of the patient for the numerous sequelae that might occur.

Although steroids possess a greater antirheumatic effect than salicylates, their use for chronic arthritic conditions leaves much to be desired, in view of their nonspecific palliative action and the likelihood of encountering serious cumulative toxic manifestations. Salicylates remain a well-recognized stand-by for the effective and safe symptomatic relief of arthritic conditions.

Statement by Dr. Hagemann:

PAUL O. HAGEMANN

THE management of rheumatoid arthritis is complicated by the lack of specific therapeutic agents and the variable and unpredictable course of the disease. This should be understood and mutually accepted by both the physician and the patient. The physician and patient who become discouraged have not adopted a factual approach to treatment. Rheumatoid arthritis is a chronic disease and the changes effected are correspondingly gradual and slow.

Treatment Plans

Three regimens are presented in table 1. The basic regimen (plan 1) for the management of patients with symptomatic and active rheumatoid arthritis includes: (1) local rest and protection of the involved joints and increased bed rest for general support; (2) active and corrective exercises performed by the patients according to definite instructions; (3) administration of salicylates, e.g., 40 gr. or 3 gm. aspirin daily; and (4) proper adjustment of nutrition. These measures will be adequate for patients with mildly active rheumatoid disease.

If this regimen does not adequately control the symptoms, more aggressive types of therapy should be considered; i.e., plan 1 should be supplemented by plan 2. This consists of (1) gold therapy,[1,2] which I believe is the

TABLE 1

THERAPEUTIC REGIMENS FOR RHEUMATOID ARTHRITIS

Plan 1 (for mildly active disease)
1. Rest
2. Active corrective exercise
3. Salicylates
4. Proper nutrition
Plan 2 (to be added to plan 1 in more active disease)
1. Gold therapy
2. Antimalarial therapy
Plan 3 (to be added to plans 1 and 2 in very active disease)
1. Steroid therapy
2. Phenylbutazone therapy

best method for altering the underlying rheumatoid process, and (2) administration of antimalarial medications[3] such as chloroquine, MEPACRINE® or hydroxychloroquine, which may have an action similar to gold. Both gold and the antimalarial agents may be expected to have a favorable effect about three months after the initiation of therapy.

If the rheumatoid process is sufficiently active and severe that the patient cannot perform his usual work, it is necessary to use agents which might favorably modify the process more rapidly. The period required for gold and the antimalarial medications to produce beneficial results is too long to be generally acceptable. Under these circumstances, therapy plan 3 should be used in addition to plans 1 and 2.

Corticosteroid Therapy

Without question, the corticosteroids[4-6] are the most effective agents we have for helping patients with active rheumatoid arthritis in a matter of days. Phenylbutazone[7] might be considered a similar agent for use in place of or along with corticosteroids. Cortisone and the newer derivatives which act as anti-inflammatory agents are useful for symptomatic relief. However, evidence at hand is sufficient to show that the rheumatoid process continues and that joint destruction can be progressive in spite of steroid administration.

Dosage—The dosage of corticosteroids should be kept as low as possible. Complications resulting from long-continued high-dosage administration are all too well known, and the universal trend is toward using smaller amounts than were given four to five years ago. The present recommendation is a dosage of 50 mg. cortisone or 8 to 10 mg. of the newer steroids such as prednisone, prednisolone, triamcinolone and methylprednisolone. Ideally, the steroids should be administered in divided doses every six to eight hours. As patients improve from treatment by plans 1 and 2, it is often possible to reduce the dosage of corticosteroids accordingly; frequently, they can be withdrawn after four to six months of gold therapy. Patients who are unable to discontinue steroid therapy because of lack of fundamental improvement generally can tolerate the afore-mentioned dosages for long periods without serious side effects. Rather than giving additional steroids, the physician should consider adding agents such as phenylbutazone, if necessary, to secure adequate symptomatic control.

Side effects—The picture of hypercortisonism, including rounding of the face, hirsutism, obesity, hypertension, etc., is now well known. This condition is highly undesirable and should be avoided because of the more serious complications which frequently ensue. Active peptic ulceration with hemorrhage and occasional perforation has been observed all too frequently in patients with hypercortisonism. Osteoporosis, particularly of the spine, is another severe and disabling complication and is often associated with painful episodes due to compression fractures of the vertebrae. Another serious side effect is the syndrome of hypercortisonism described by Slocumb[8] and characterized by muscle and joint aches, weakness, fatigue, irritability and poor endurance. The symptoms temporarily relieved by increased steroid dosage invariably recur; thus, a vicious circle with increasing

hypercortisonism and increasing steroid dosage is established. Malignant rheumatoid arthritis, lupus erythematosus or periarteritis nodosa eventually develops in a significant percentage of patients with hypercortisonism. Many have positive reactions to L.E. tests. Apparently, the influence of large amounts of steroids breaks down the body's defense against collagen disease, and florid and fatal disease may develop. The possibility of such major complications makes it difficult to take the risk of giving large dosages of steroids over a period of months.

Conclusion

It is imperative that the physician follow an orderly plan in managing patients with rheumatoid arthritis. The steps which have been outlined seem to constitute an approach that will afford the patient the best opportunity for improvement.

Far too frequently, the physician sees patients with rheumatoid arthritis who are being treated only with steroids. This inadequate therapeutic program is partly the fault of the physician who does not insist on the patient's resting, exercising and taking salicylates regularly, and partly the fault of the patient, who naturally is most interested in symptomatic relief. We are not fulfilling our obligations as physicians if we allow our patients to discontinue the procedures outlined in plan 1. The patient must learn that he has to live and work with this disease and that taking a few steroid tablets each day is a totally inadequate approach to the over-all problem.

Steroids should be employed for symptomatic relief in patients who are not adequately controlled by the methods outlined in plan 1 and who are too uncomfortable and incapacitated to wait for possible benefit from gold or antimalarial therapy (plan 2). If patients improve from plans 1 and 2, steroid therapy gradually can be withdrawn in a matter of months. In those who fail to respond adequately to the therapy outlined in plans 1 and 2, the steroid dosage mentioned previously is not sufficient to produce complications that are more serious and incapacitating than the underlying condition.

REFERENCES

1. Smith, R. T. et al.: Increasing the effectiveness of gold therapy in rheumatoid arthritis. J.A.M.A. 167: 1197-1204 (July 5) 1958.
2. Lockie, L. M., Norcross, B. M. and Riordan, F. J.: Gold in the treatment of rheumatoid arthritis. *Ibid.*, pp. 1204-1207.
3. Scherbel, A. L. et al.: Comparison of effects of two antimalarial agents, hydroxychloroquine sulfate and chloroquine phosphate, in patients with rheumatoid arthritis. Cleveland Clin. Quart. 24:98-104 (April) 1957.
4. Ward, L. E., Polley, H. F., Slocumb, C. H. and Hench, P. S.: Cortisone in the treatment of rheumatoid arthritis. J.A.M.A. 152:119, 1953.
5. Ward, L. E., Slocumb, C. H., Polley, H. F., Kendall, E. C. and Hench, P. S.: Clinical effects of cortisone administered orally to 100 patients with rheumatoid arthritis. Ann. Rheumat. Dis. 10:477 (December) 1951.
6. Freyberg, R. H., Berntsen, C. A. and Hellman, L.: Further experiences with Δ1, 9 alpha fluoro, 16 alpha hydroxyhydrocortisone (triamcinolone) in treatment of patients with rheumatoid arthritis. Arthritis and Rheumatism 1:215-229 (June) 1958.
7. Kuzell, W. C. et al.: Phenylbutazone; further clinical evaluation. A.M.A. Arch. Int. Med. 92:646 (November) 1953.
8. Slocumb, C. H. et al.: Diagnosis, treatment and prevention of chronic hypercortisonism in patients with rheumatoid arthritis. Ann. Int. Med. 46:86-101 (January) 1957.
9. Kemper, J. W. et al.: The relationship of therapy with cortisone to the incidence of vascular lesions in rheumatoid arthritis. Ann. Int. Med. 46:831-851 (May) 1957.

Comment by Dr. Batterman:

Regardless of the severity of rheumatoid arthritis, the basic principles of therapy are the same for all patients. These include (1) specific therapy which, in my opinion, is obtained at the present time only by gold compounds; (2) measures for symptomatic relief, including antirheumatic drugs, all corticosteroids, analgesics, physical therapy, liniments and anesthetic agents; (3) measures for preventing or correcting deformities, or both; (4) supportive therapy, which involves nutrition and administration of iron and vitamins; and (5) psychotherapy as required.

Although corticosteroids provide effective and immediate relief, their cumulative toxicity and their pharmacologic inhibition of other therapeutic agents, such as gold and the salicylates, limit their usefulness except in an unusual patient. The proper utilization of salicylates and symptomatic medicaments, other

than corticosteroids, employed simultaneously with gold therapy offers the greatest likelihood of prolonged, clinical safe control of the rheumatoid process.

Comment by Dr. Hagemann:

The statements made by Dr. Batterman agree essentially with my own. One cannot disagree with the comment that steroids are symptomatic agents or with the statement that results of steroid therapy are ". . . not conducive to *unqualified* recommendation. . . ." Is it not wise then to use a potent agent for symptomatic relief, limiting the dosage so that the disadvantages of larger doses are essentially avoided? One must be content with submaximal relief of symptoms, using salicylates plus small amounts of steroids in the dosage levels outlined previously. In our clinic we have abandoned the original plan of initiating steroid therapy with large doses, which are later reduced, in favor of the more realistic and safer approach.

In all of medicine, one must balance the risk of therapy against the risk of disease; this principle applies to the use of gold and steroids, and even salicylates, although admittedly to a lesser degree.

MEETINGS and Postgraduate Courses

AMERICAN COLLEGE OF CHEST PHYSICIANS, PHILADELPHIA: Postgraduate course on diseases of the chest, March 30-April 3, at the Sheraton Hotel. For further information, write to: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11.

AMERICAN COLLEGE OF CHEST PHYSICIANS, SAN FRANCISCO: Fourth annual postgraduate course on diseases of the chest, February 16-20, at the Sir Francis Drake Hotel. For further information, write to: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11.

TEMPLE UNIVERSITY SCHOOL OF MEDICINE, PHILADELPHIA: Forty clinics in clinical endocrinology and metabolism, starting March 25. For further information, write to: Office of the Dean, Temple University School of Medicine, Philadelphia. Third annual course on recent advances in medicine, beginning October 21. For further information, write to: Dr. Albert J. Finestone, Temple University Medical Center, Philadelphia.

UNIVERSITY OF KANSAS MEDICAL CENTER, KANSAS CITY: A one year fellowship in clinical hematology is available primarily to those interested in academic medicine and teaching. The fellowship begins July 1, 1959 and provides a stipend of $3600. For further information, write to: Dr. Sloan J. Wilson, Director, Hematology Section, Department of Internal Medicine, University of Kansas Medical Center, Kansas City 12.

UNIVERSITY OF KANSAS SCHOOL OF MEDICINE, KANSAS CITY, KANSAS: Postgraduate courses to be presented at the following centers during 1959:

University of Kansas Medical Center, Kansas City
- Operative clinics
  - Peripheral vascular disease, February 11
  - General surgery, March 18
- Symposia
  - Psychosomatic problems, February 19
  - Modern medicine, March 19
  - Medical and surgical emergencies, April 16

Moila Temple, St. Joseph, Missouri
- Erythropoietic plasma factor: Its relation to anemias and polycythemias, February 17
- Garden-variety diseases, March 17
- Fluid-electrolyte replacement therapy, April 21

Southeast Kansas Tuberculosis Hospital, Chanute
- Fluid-electrolyte replacement therapy, February 17
- Hormonal physiology and therapy during pregnancy, March 17
- Garden-variety diseases, April 21

For further information, write to: Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 12.

WESTERN REGIONAL MEETING, AMERICAN GROUP PSYCHOTHERAPY ASSOCIATION, SAN FRANCISCO: April 2-3, at the Sheraton-Palace Hotel. For further information, write to: Dr. Donald A. Shaskan, Veterans Administration Mental Hygiene Clinic, 49 Fourth Street, San Francisco.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Report of Case

DR. CHARLES B. PUESTOW (chief, surgical service): A 55 year old white man with a history of seven episodes of gastrointestinal bleeding, ulcer of 10 years' duration, hypertension, and carcinoma of the sigmoid with metastases to regional lymph nodes was admitted to Hines Veterans Administration Hospital in February 1955. In 1952 an abdominoperineal resection had been done, and there had not been any clinical evidence of recurrence of carcinoma. The seventh episode of gastrointestinal bleeding had occurred in August 1954, and x-rays at that time disclosed scarring of the duodenum. Prior to admission the patient noted a black, tarry stool from his colostomy and had symptoms of syncope. Blood pressure was 190/128 at the time of admission.

With medical management, the gastrointestinal bleeding stopped within 24 hours. X-rays did not reveal an actual ulcer crater but there was duodenal deformity. A roentgenographic series of the small bowel gave negative findings. The patient was scheduled for gastric resection.

On February 11, 1955, subtotal gastric resection of the posterior Billroth II type with a Polya type of closure was performed. The following day the Levin tube drained dark bile but the patient complained of cramping abdominal pain. On February 13, the second postoperative day, shock ensued, coinciding with sudden increase in bloody aspiration from the stomach; a few clots were present. The patient vomited about 250 cc. of gastric fluid. He was given 1000 cc. of blood and his condition improved markedly. A consultant advised immediate reoperation with exploration of the anastomotic site. This was done, and a bleeding vessel was found at the junction of the greater curvature and the jejunum, with a small associated hematoma on the gastric side of the anastomosis. This was sutured, and Penrose drains were placed in the left upper quadrant subcutaneously. The patient's condition was fair during the night. He received a total of 4 pt. of blood on the day of operation. Postoperatively the drainage with Levin suction was almost entirely bile.

The patient's condition appeared favorable until February 16 (three days after the second operation, five days after the first), when jaundice was noted. Stools were dark, the colostomy was functioning well, and he began to take all feedings. He complained of pain in the right upper abdominal quadrant and also in the right shoulder on February 18. The jaundice appeared to be stabilized, but bile was draining from the Penrose drain in the right upper quadrant and it was felt that the duodenal stump probably was leaking.

On February 19 the leukocyte count was 25,900. Erythrocyte count was 4,600,000, and hemoglobin was 13 gm. Blood pressure fell to 60/0, the pulse rate rose to 168, and the patient was extremely weak, pale and dyspneic and perspired profusely. Oxygen was given,

and his condition remained somewhat precarious for two to three hours. A consultant advised reoperation, and 3 pt. of blood were ordered. Vital signs finally were stabilized and the patient was taken to the operating room. Exploratory laparotomy under general anesthesia revealed a large collection of fluid beneath the liver. A leak could not be found from the stomach or the duodenum. A double-lumen tube was inserted into the distal limb of the gastrojejunostomy anastomosis.

Postoperatively the patient's condition remained precarious. The colostomy began to function well. He remained jaundiced. A Stedman sump pump was used to produce suction down to the duodenal stump.

By February 24 the patient's condition had deteriorated markedly. The direct Van den Bergh reaction was 12, and the indirect 5.2. It was felt that acute hemorrhagic pancreatitis probably was present, with a poor prognosis. The patient died on February 24, 13 days after the first operation.

Discussion and Differential Diagnosis

This man had a history of ulcer and seven episodes of gastrointestinal bleeding. I presume, since many roentgenographic series of the gastrointestinal tract had been made, that an ulcer had been demonstrated throughout this period. Three years before his final hospitalization he underwent operation because of carcinoma of the colon, and metastases were present. The basis of the recent hemorrhage possibly could have been metastases from the carcinoma, with invasion of some other part of the upper alimentary tract, but this would have been noted at operation. After gastric resection, he did not have blood in the stomach for two days. Blood was first noted 48 hours after operation, and at that time bleeding appeared to be profuse. Had he had a gastroenterostomy we might have felt that the bleeding was coming from the original ulcer. There was no mention of finding an ulcer at the time of operation. It is possible that bleeding occurred from the original ulcer and the blood passed through the anastomosis back into the stomach, but that is less likely. However, with a double-lumen tube the aspirating part may have descended into the jejunum and could have brought blood from that area. In other words, bleeding from an anastomotic site is not a common thing to occur 48 hours after operation when up to that time the contents do not contain blood.

There has been a good deal of argument as to the management of ulcer when there is a history of bleeding. Some surgeons maintain that gastric resection is all that is necessary. Others, myself included, feel that if profuse bleeding has occurred and there is bleeding at the time of operation the bleeding itself must be controlled.

So there is the possibility of recurrence of bleeding from the ulcer, the blood passing into the stomach or being aspirated from the jejunum, or bleeding from the anastomotic site. The surgeon who performed the exploratory operation stated that he did find the bleeding vessel and that there was a hematoma on the gastric side. Hematomas on the gastric side are not unusual, and generally result from a suturing of the outer row and the puncture of vessels at that time. An actual bleeding vessel, bleeding into the lumen, is not a common thing in cases in which bleeding does not occur in the first 48 hours. My technic is to evert the anterior edge with the inner row of sutures to make sure there are no bleeding vessels which could be inverted into the stomach at the time a Connell-type suture is applied. However, in view of the absence of bleeding in the first 48 hours it does not seem likely that there was such a bleeding vessel.

The patient received 1000 cc. of blood at the time of the first operation and four transfusions at the time of the second operation. Three pints of blood were ready at the time of the third operation, for a total of at least 4500 cc. or 9 pt. of blood. The jaundice that developed probably was a serum reaction and I believe it was partly responsible for the subsequent course. In the face of massive hemorrhage it may have been necessary to give that much blood. The hemoglobin level rose to 13 gm. and the erythrocyte count went up to 4,600,000, so at least blood was not spared in this case; less might have caused less reaction.

The patient complained of pain in the right

upper abdominal quadrant and the right shoulder, and the jaundice appeared stabilized, but bile was draining from the Penrose drain in the right upper quadrant and it was felt that the duodenal stump probably was leaking. It probably was not bile from the biliary tract, because drainage of pure bile would not occur unless there was an opening in the extrahepatic system or in the side of the anastomosis. In a jaundiced patient a collection of serum or other contents within the peritoneal cavity is very likely to be stained with bile pigment; that may explain the interpretation that there was a leaking duodenal stump.

I was told that there was an acute pancreatitis at the time and that it was felt that the pancreatic duct possibly may have been damaged at the time of resection. This patient had a profuse hemorrhage with a downhill course and died. I rather doubt that the bleeding which occurred 48 hours after operation was actually from the bleeding vessel at the anastomotic site. I think it was from the lesion that had produced repeated hemorrhages and had produced the bleeding prior to the patient's admission to the hospital. That lesion may well have been an ulcer in the duodenum.

I am reminded of a patient who had a similar history and whose x-rays reportedly were negative. We performed an exploratory laparotomy and could find nothing in the duodenum. The patient had a massive hemorrhage and died. At autopsy we found a large duodenal ulcer at the lower portion of the duodenum as it rounded the curve below the head of the pancreas. The ulcer had eroded through, formed an abscess between the pancreas and the duodenum, and eroded a large artery in that area, producing severe hemorrhage. Such an ulcer is very difficult to demonstrate at operation. Later, reviewing the x-rays with the radiologist, we found a large crater down at the lower end of the duodenum, at the site of the ulcer, but the radiologist said he had felt it was a markedly dilated ampulla of Vater. However, it was well below the ampulla of Vater. I mention that case because it brings out another location for trouble in this area that we must consider.

In view of the history of malignancy, we could think the patient had a recurrence of carcinoma, but this is unlikely. The surgeons did not find evidence of such a recurrence, and the hemorrhages predated the carcinoma. It is my opinion that this patient had a lesion which was not corrected at the first operation, which had produced repeated hemorrhages before operation, and which was responsible for the subsequent hemorrhages. It could be a low-lying duodenal ulcer, in view of the history and the x-ray findings. It is mentioned that a definite ulcer crater was not demonstrated but there was duodenal deformity. One does not expect to find bleeding of this magnitude and repeated this often without being able to demonstrate more in the way of roentgenologic findings than were reported in this case. My conclusion is that this man had a lesion of the small bowel which bled despite the gastric resection, and that it caused his death.

Dr. Charles Mayo used to say that if an operation had to be done a second time the mortality was likely to be about 50 per cent, and if a third operation had to be done the mortality was 75 per cent. The moral is that one must do everything possible at the first operation. Another detrimental factor in this case was the apparent hepatitis from a transfusion reaction, further impairing the possibility of recovery.

Roentgenologic, Surgical and Postmortem Findings

RADIOLOGIST: A roentgenogram of the colon made August 12, 1952, showed an annular filling defect in the region of the sigmoid colon which was subsequently shown to be a carcinoma. Barium enema studies after abdominoperineal resection did not show evidence of recurrence. A roentgenogram made in December 1953 disclosed a definite prolapse of gastric mucosa into the base of the duodenal bulb with a small niche on the lesser curvature and perhaps some annular constriction near the apex of the bulb. These findings are not diagnostic of an ulcer crater but suggest ulcer deformity. Roentgenologic examination during the final period of hospitalization, in February 1955, showed some deformity of the bulb with an annular constriction near the

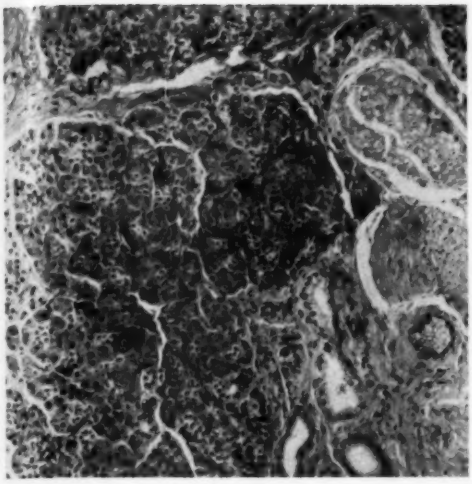

FIGURE 1. Section of duodenum showing pancreatic tissue surrounded by muscular tissue.

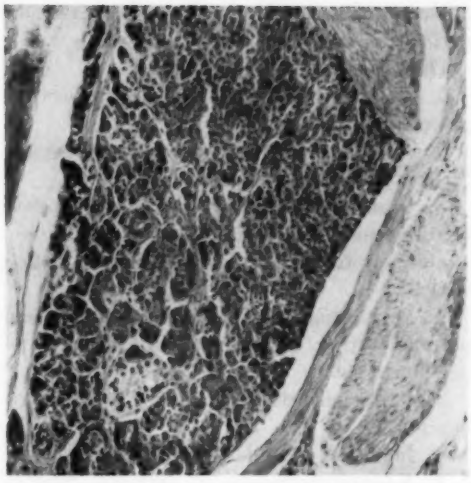

FIGURE 2. Aberrant pancreas with islet tissue at the lower end of section.

apex, prominent transverse folds in the second portion of the duodenum, and what appeared to be redundancy in the second portion.

DR. HEINMILLER (pathologist): The presence of metastases to the regional lymph nodes in 1952 was confirmed histologically.

The surgical specimen of the gastric resection showed a mass in the wall of the first portion of the duodenum. The operative note stated that the clamp apparently had gone through the edge of an ulcer. The first sections which were taken did not show this ulcer, nor did repeated sections. Figure 1 is a photomicrograph of the section of duodenum containing the mass. One sees the muscle of the duodenum, and glandular tissue infiltrating and growing through the muscle. These are gland structures. Figure 2 is a higher-power view. The gland tissue growing in the wall is identified here as pancreas, even to the extent of showing normal islets of Langerhans.

An autopsy specimen of the pancreas did not show evidence of pancreatitis. An incidental finding was a leiomyoma in the wall of the stomach.

The skin was icteric. The lower half of the peritoneal surface was smooth. The right upper portion of the abdomen contained about 500 cc. of dark, bile-stained fluid. The large colon was markedly distended, especially the cecal area. The entire small intestine was distended. The sigmoid and rectum were surgically absent. The upper peritoneum was markedly different from the lower. The line of demarcation was the transverse colon and its mesocolon. Above was an extensive inflammatory change involving all peritoneal surfaces. The pancreas weighed 110 gm., normal lobulations were maintained throughout, and a probe was inserted through the duct of Wirsung without evidence of obstruction.

The stomach was dilated and contained approximately 1000 gm. of dark gray material. A posterior Polya gastroenterostomy was inspected and there was no evidence of disruption of the suture line, which appeared to be healed. Methylene blue was injected into the third portion of the duodenum, and the dye was immediately apparent in the lesser peritoneal sac, coming from what appeared to be a minute opening in the duodenal stump. Sections of the duodenal stump revealed catgut suture material which passed through the duodenal wall at the point which appeared grossly to contain aberrant pancreatic tissue. There was a colostomy opening from the descending colon on the left side of the abdomen. The large colon appeared normal. There was no

evidence of tumor implants on the peritoneal surfaces or in the nodes.

Our diagnoses are as follows.

1. Duodenal ulcer. Status: postresection, gastric.

2. Aberrant pancreatic tissue in duodenum. Status: postresection, gastric.

3. Gastrointestinal hemorrhage, secondary to diagnosis number 1. Status: postlaparotomy, exploratory, with ligation of the bleeding vessels.

4. Peritonitis, secondary to above. Status: postexploration, abdominal, with drainage of peritoneal cavity.

5. Duodenal fistula, secondary to diagnosis number 1.

6. Jaundice, secondary to above.

7. Adenocarcinoma of sigmoid. Status: postresection, abdominal; no evidence of recurrence present.

Comment

DR. KIRSCH (consultant in radiology): We did not recognize this aberrant pancreas even on reviewing the films. I believe its hemorrhage was a distinct factor in the history. We consistently considered this a duodenal ulcer. On several occasions we could see what looked like a crater. But it may be that this constriction that we called an annular deformity due to the ulcer actually was the aberrant pancreas.

Dr. Benner studied a group of cases of aberrant pancreas in the stomach and called our attention to a feature they all had in common. Then we reviewed the films and Dr. Littner and I reported a series of seven cases of aberrant pancreas in the stomach. In practically all the cases there was a very sharply outlined defect in the antrum, and in most of them there was a central fleck or depression, simulating an ulcer. Only one of the patients had hemorrhage, and in that case there was a duodenal ulcer to explain the hemorrhage. In fact, the central depression which originally had been considered an ulceration was shown by Dr. Benner to be not an ulcer at all; it was completely covered with mucous membrane and was the receptacle of some of the pancreatic duct, so I fail to see how aberrant pancreas, without associated lesions, could explain the hemorrhage. Most of these patients had symptoms which simulated an ulcer or a tumor. There was nothing very typical about them. We thought if one could make the distinction radiologically and diagnose aberrant pancreas in the stomach, it might help the surgeon, who could perhaps choose an operation suited to this type of lesion rather than operate for gastric malignancy. In one case the lesion was suspected; it was considered an intramural lesion, and that was one of the possibilities.

We have had two cases of aberrant pancreas in the duodenum, one in the first portion of the duodenum and the other in the region of the ampulla of Vater. The latter presented clinically as a tumor of the ampulla of Vater but turned out histologically to be aberrant pancreas.

DR. PUESTOW: I think we can learn something from these cases. In operating on any patient with ulcer, particularly an ulcer associated with repeated episodes of bleeding or with massive hemorrhage, we should not operate with a preconceived idea of what we are going to do. We should have an open mind and should thoroughly examine the duodenum before starting any procedure. If there is any question of the lesion, it is simple to open the anterior wall of the duodenum and look inside before starting a gastric resection or whatever procedure you were going to do. I do not know whether or not the aberrant pancreas in this case could have been palpated, but perhaps a careful exploration might have revealed something to prompt the surgeon to incise the duodenum and look inside before doing a major resection. When you place a clamp across tissue whose nature is suspicious it would be well to remove the clamp and look into the duodenum and explore it before oversewing it. Frequently we will do an open operation on the duodenum, especially when we suspect a bleeding ulcer, so that we can ligate any vessels present or better understand what we are dealing with. It is so simple to open the anterior wall of the duodenum and split it down for some distance so that one can get a thorough view; then one feels much safer in determining the procedure to be carried out.

Medical Progress 1958

MORRIS FISHBEIN*

Chicago

BIOCHEMISTRY and genetics offered outstanding advances in medicine during 1958, and the award of the Nobel prize to Drs. Edward L. Tatum, George Beadle and Joshua Lederberg was a recognition of this advancement. Biochemical studies of genes and of viruses indicated a similar constitution, with nucleic acid at the center, surrounded by proteins of varied structure and form. Greater understanding has led to the concept that such relationships may be the basis of cancer in human beings and, perhaps, the secret of life itself. The technics of tissue culture, the ability to isolate and to study individual cells of the brain and of various organs of the body, and the use of automation in facilitating chemical studies of living tissues all contributed greatly to medical progress and established trends toward the future. The infectious diseases apparently are either conquered or are approaching extinction and are no longer the threat to life and health that they were in the first part of this century.

The problems that greatly concerned medicine in 1958 were diathetic and metabolic disorders such as rheumatism and gout and degenerative disorders such as those that lead to the aging process and to failure of the kidney, heart and brain. In all of these fields research is being stimulated now on a large scale, and results appear with a speed never contemplated 50 years ago. New studies of the glands, particularly the pituitary gland, are yielding factors which control the growth of the human body, pigmentation, and many other functions. The relationship between glandular activity and the growth of cancer is becoming well established.

Cancer

Cancers of the breast and the prostate have been proved to be "hormone dependent." The removal of the pituitary gland can prevent the production of new cancer cells in the breast and the prostate. Surgical removal of the pituitary gland has been found effective in stopping the flow of hormones from the pituitary to the tissues. However, such surgical removal is exceedingly hazardous and difficult. In Glasgow, removal of the pituitary was effected by inserting two glass seeds containing radon directly into the gland. By the radioactive action the production of hormones was stopped. At the University of Chicago, a cancer research team has now improved the procedure by using a new radioactive substance, oxide of yttrium, made into beads smaller than the head of a pin. The yttrium is made radioactive in the atomic ovens of the Argonne National Laboratory. Fifty patients have been treated by insertion of such radioactive seeds into the pitui-

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tary, with results comparable to those obtained by surgical removal of the pituitary gland.

After the pituitary gland is removed, its essential functions are supplied by the oral administration of cortisone and thyroid hormones which are not involved in the cancer-stimulating effect. By another innovation the beads may be placed into the pituitary through a needle passed through the nose, with the procedure controlled by simultaneous visualization of the technic through the Phillips image-intensifying fluoroscope, an x-ray device.

During early experiments in the manufacture of penicillin, by-products were observed which could destroy cancer cells. These by-products have never been suitably rediscovered or isolated. Under the direction of the Cancer Chemotherapy National Service Center of the National Institutes of Health, Bethesda, Maryland, many pharmaceutical and chemical organizations are now screening and evaluating thousands of synthetic compounds and culture filtrates resulting from the manufacture of antibiotics in an attempt to find a drug that will be specific against cancer. Over 50,000 such materials are being screened. Some anticancer activity has been discovered in more than 100 materials. The program, which began as a joint effort of industry and government in May 1956, has thus far been concerned with 20,000 synthetic chemical compounds and over 30,000 antibiotic culture filtrates. The materials are being tested in three types of tumors found in mice. About two million animals are used yearly in these studies. At present, 100 industrial companies are participating in the program under governmental contract. One-third of these are pharmaceutical companies. Six large pharmaceutical companies are screening compounds on their own initiative. In addition, 400 hormone substances are now being screened and evaluated.

With progress against cancer, the likelihood of cure has changed from one in seven cases in 1938 to one in three cases in 1958. Many studies are being made of the resistance of the tissues of the body to cancer. Experiments are being made with transplants of cancer cells, and the concept of immunity to cancer caused by the biochemical nature of the tissues is gaining ground. Moreover, viruses are being definitely related to the incidence of some forms of leukemia.

Surgery

Improvements in surgery indicate progress in both surgical technics and the reconstructive surgery related to physiology. Surgical procedures have been developed for treating apoplexy or strokes which involve control of the circulation, and actual attempts are being made to remove the hemorrhages and the clots. Similar procedures are being used for obstruction of the renal artery in cases of high blood pressure. Technics are being developed for surgery of the heart and for aneurysms, which would have been inconceivable without the development of the heart-lung machine, which permits circulation of the blood outside the body so that the surgeon may operate on a dry heart, and without the use of potassium citrate to promote drying of the tissue.

Anxiety and Heart Disease

Anxiety caused by emotional stress is especially undesirable for anyone with heart disease. At the Cardiac Clinic of Long Island College Hospital, 80 patients with various forms of heart disease were treated with tranquilizing drugs. The medication definitely reduced their nervous tension and anxiety. In cases of coronary thrombosis in which the circulation to the muscle of the heart had been blocked extensively, the progress of the disease was not found altered by production of tranquility.

In a similar study carried on at the Postgraduate Medical School in London, investigators proved by measuring blood volume in the fingers that emotional factors can cause constriction of the blood vessels and that elimination of anxiety and stress by the use of tranquilization results in dilation of these blood vessels. Complete mental relaxation occurs in sleep except in the presence of disturbances induced by dreams.

At the meeting of the American Heart Association in late October, physicians reported that hard-driving men have higher levels of

cholesterol, faster blood-clotting time, and six to eight times as much clinical heart disease as have men with the opposite type of personality. The behavior pattern of the person likely to have heart disease includes intensive drive, profound inclination to compete, persistent desire for recognition and advancement, continuous involvement in functions subject to time restrictions or deadlines, habitual compulsion to accelerate the rate of execution of physical and mental functions, and superior mental and physical alertness. Native-born Americans have been found to be significantly more susceptible to coronary disease than are foreign-born workers. Investigators at the University of North Carolina found that disturbing emotions tend to push an increased amount of blood back to the heart by raising the pressure and tension in the small veins most remote from the heart.

Ophthalmology

In Spain, Barraquer injected alpha-chymotrypsin into the eye. Injection of this substance frees the lens so that it can be lifted out by suction, making the operation for cataract much easier.

Experiments continue in an effort to use plastics for making artificial lenses and for replacing the lens of the eye affected by cataract.

New Drugs

Among the new drugs which have been developed in recent years, outstanding is chlorothiazide, also known as DIURIL®, which eliminates fluid from the body and lowers the blood pressure. Many improvements have been made in hormones, so that their beneficial effects are in antagonizing other hormones. For instance, an estrogen has been found which can antagonize androgens without having a feminizing effect on the person in whom they are used. This is especially important because of the large doses of estrogens used in treating cancer of the prostate.

Endocrinologists report the isolation from the pineal gland of a substance called melatonin, which is capable of lightening the dark shade of skin. Similarly, the pituitary gland contains the melanocyte-stimulating hormone, which is also involved in pigmentation.

In treating certain cases of diabetes several orally administered preparations are now being used to replace insulin. The best-known is ORINASE®. However, another new product called DIABINESE® has been developed; this is chlorpropamide whereas the previously mentioned preparations are based on sulfur.

Cortisone derivatives used in treating arthritis are being continually improved. New preparations have been developed which have the same efficiency as METICORTEN® but do not interfere in any way with the water balance in the body. The most thoroughly studied thus far is DECADRON® or DERONIL®.

The number of tranquilizing drugs and muscle relaxants continues to increase.

In the treatment of cancer, particularly the choriocarcinoma, which forms in the female genital tract, a drug called Methotrexate has been used with success at the National Cancer Institute.[1] In 5 of 19 cases a complete remission was observed; there were partial remissions in seven and transient remissions in 10 of the cases.

Plasmin, a clot-dissolving enzyme, has been used to treat clots which block circulation in the arms and legs and also to treat clots in the heart. In animal experiments clots in the heart were seen to begin dissolving within four to eight hours after injection of plasmin into the circulation. Striking results in dissolving blood clots in various parts of the body are also credited to a new drug called ACTASE®, which is known as fibrinolysin.

In a wide variety of disorders affecting the skin, cortisone preparations have continued to prove useful. A new preparation, triamcinolone acetonide, known as KENALOG®, was found preferable to cortisone ointments in many patients with a variety of skin disorders.

A symposium on antibiotic drugs held in October[2] showed that more than 2,500,000 lb. of antibiotics are purchased annually in the United States. Among the newer antibiotics is kanamycin sulfate, which has been widely used for a variety of infectious disorders. Kanamycin is a discovery originally made by Dr. Hamao Umezawa of the University of Tokyo, Japan.

Another antibiotic announced is a broad-spectrum substance called ACTINOBOLIN®, which in experimental studies showed activity against a number of infections and against experimental cancers. It was not effective against tuberculosis.

At the same time great concern is being expressed over increasing staphylococcal infections (particularly in hospitals), apparently resulting from organisms' becoming resistant to antibiotics.

Significant is the development of a four-in-one shot designed to immunize children against poliomyelitis, whooping cough, diphtheria and tetanus. Such a preparation, known as QUADROGEN®, was tested successfully in approximately 300 children in Detroit.

In the survey of antibiotics new compounds were described called sulfonyl hydrazones, which are related to the sulfonamides and exert special activity against staphylococci.

A modification was made of para-aminosalicylic acid which appears to cause less gastric disturbance. This product is called PASTEBAMIN® or phenyl p-aminosalicylic acid.

Rheumatoid Factor

Many physicians believe that there is an abnormal substance in the blood of people who have rheumatoid arthritis and they named it the "rheumatoid factor." Dr. Russell L. Cecil, a pioneer in research on arthritis, says that this factor is likely to be identified and its actual structure determined in the near future. In this way the actual cause of rheumatoid arthritis, which is at present unknown, may be detected. Tests for the presence of rheumatoid arthritis now being conducted in many laboratories depend on the interaction of gamma globulin from a rheumatic patient's blood with that from persons who do not have rheumatism. Particles of latex or certain common clays may be coated with gamma globulin from the blood of normal people. When this material is mixed with serum from a person who has rheumatoid arthritis, the particles agglutinate. The substance that causes this reaction is the rheumatoid factor. When this substance is isolated in quantity, identified, and its structure determined, the biologic chemists will know whether it is an enzyme, an antibody or something of another class.

The rheumatoid factor in the blood of persons with rheumatoid arthritis appears to contain three different proteins. Injection of rheumatoid factor proteins into man and animal failed to produce the disease, so that this does not appear to be the causative factor; however, it is obviously of value in diagnosing the disease.

Common Cold

In the University of Illinois Medical School infectious secretions were taken from people with the common cold and transferred to the noses of volunteers for the experiment. Colds developed in 45 per cent of 143 people with allergies and in 31 per cent of 693 people without allergies. Neither tobacco smoking nor previous removal of tonsils had any relationship to the development of colds. Apparently, women are especially susceptible to colds if they are chilled during the middle third of the menstrual cycle; colds developed under such circumstances in 77 per cent of women tested. Women have colds more frequently than men. Apparently, the chilling was a definite factor in lowering resistance.

Brain Waves and Spasms

By use of the electroencephalograph, unusual brain waves called hypsarrhythmia have been noted by the Drs. Gibbs, Brain Research Foundation, Chicago. These waves, which are of a special type, appear in children who have twitching of the muscles and rolling of the eyes, with a tendency toward mental retardation. The condition is called infantile myoclonus. In general, such infants have tended to become more and more retarded and to die at early ages. In the University of Louvain, Belgium, Dr. Soler discovered that regular doses of ACTH either completely cured the condition or were of great benefit. The exact cause of the condition has not been definitely determined, but it is perhaps related to complications of infections and sensitization of the body to its own damaged brain tissue. Previously, such patients had not been benefited by any form of medical treatment.

Hiatal Hernia

When a portion of the stomach passes through the diaphragm into the chest cavity at the point where the esophagus or swallowing tube enters the abdomen, the condition is called diaphragmatic or hiatal hernia. Before the development of the x-ray the condition was practically never diagnosed. More recently it has been found frequently, particularly in persons more than 50 years of age. In a series of 2,402 x-ray studies of the esophagus and stomach, 300 such cases were found. By contrast, the incidence of gallstones is generally 18 per cent and of duodenal ulcer 13 per cent. Ninety-five per cent of all patients report that the chief symptoms of hiatal hernia are feelings of discomfort in and fullness or distention of the abdomen, griping, and burning or pain under the breast bone or high on the left side. Unlike ulcer pain, these symptoms do not appear regularly or periodically in relationship to eating, but are uninfluenced by food. The symptoms may persist for seconds, minutes or hours and, sometimes, even for days. Occasionally the condition is confused with pains related to the heart. The symptoms are aggravated by lying on the back and often are brought on by leaning forward, bending or by any other movement that increases the intra-abdominal pressure; hence, they are relieved by standing upright and by exhaling deeply. The symptoms become worse under conditions of nervous tension. In exceedingly severe cases surgical intervention is necessary to cure the condition, as with any other hernia or rupture. Recommendations for relief include lying in a propped-up position at night, avoiding heavy evening meals, the use of antispasmodic drugs, and taking sedatives which are prescribed by the physician.

Decorroding Hardened Arteries

In San Francisco, investigators for the California Heart Association found that if lecithin is continuously injected in rabbits with hardening of the arteries it causes the characteristic patches of this disease to disappear.[3] Lecithin is a complex chemical found in egg yolk, brain, bile and similar substances. At the University of Pittsburgh, purified lecithin was successful in dissolving the plaques in rabbits and dogs with atherosclerosis. Thus far, a suitable method for removing these fatty patches that roughen and narrow the inside of blood vessels in hardening of the arteries has not been found. The taking of corn oil can cause a drop in the total cholesterol in the blood. However, after some months, the usual quantity of cholesterol returns to the blood, even though the corn oil is continued. After reviewing all the methods now known for preventing hardening of the arteries, a leading investigator said four conditions are necessary for preventing this condition: (1) Select ancestors who have lived long; (2) be a woman, preferably less than 45 years old; (3) eat a normal diet with limited calories, normal protein and less than 25 per cent calories from fat; and (4) solve emotional problems some other way than by overeating or developing high blood pressure.

Artificial Respiration

Resumption of breathing after suffocation, electric shock or drowning is stimulated by artificial respiration. Until recently, the method officially recommended was the Holger Nielsen or back-pressure arm-lift method. Now, most authorities are convinced that the most effective method is mouth-to-mouth artificial respiration.[4] The person's head is turned to the side and the throat is cleaned by wiping it out with fingers or handkerchief or by suction. Then a thumb is put between the person's teeth and the jaw is pulled forcibly upward. The mouth should not be opened widely, because it must be covered entirely by the operator's mouth. The operator holds the person's nose with his other hand. The operator then takes a deep breath, puts his mouth and thumb firmly over the person's mouth, and blows (forcefully in adults and gently in children), watching the chest at all times. As soon as the chest rises, the operator removes his mouth from the person's mouth and permits the suffocated person to breathe out the air by the elastic recoil of the lungs and chest wall. If the operator fails to see the chest rise or if he hears rumbling of air in the stomach, he must improve his support of the jaw which

holds open the air passage. If this also fails to initiate a rise of the chest, he blows more forcefully, using greater volume and pressure. The blowing to inflate the chest must be deep and is repeated at a rate of 20 per minute. A special S-shaped device has been developed which provides a mouthpiece for the operator, the other end going into the breathing passage. This artificial airway should be made easily available to fire fighters, ambulance and Red Cross personnel, policemen, beach guards, doctors and nurses. Hospital physicians can carry such airways as a part of their regular equipment. Extensive research at the University of Illinois College of Medicine demonstrated that the mouth-to-mouth technic is "unequivocally superior" to the manual technics.

Medical Students and Medical Schools

During the years 1957 and 1958, American medical colleges enrolled 29,473 students. The number of medical schools in the United States has increased to 85, of which 60 report major construction for controlling obsolescence. During 1957 and 1958 the medical schools spent $275 million, an increase of 13 per cent over the preceding year. At present in the United States, there are 78 approved four year medical schools and four two year schools in the basic medical sciences. In addition, three schools are in the process of development and will be graduating students in the near future. In 1948 there were 77 schools, of which seven were two year schools. In 1957, 6,796 physicians were graduated; in 1958, 6,861. The number of freshmen was the largest in history, namely, 8,030, an increase from 6,487 in 1948.

REFERENCES

1. Hertz, R., Bergenstal, D. M., Lipsett, M. B., Price, E. B. and Hilbish, T. F.: Chemotherapy of choriocarcinoma and related trophoblastic tumors in women. J.A.M.A. 168:845 (October 18) 1958.
2. Sixth Annual Symposium on Antibiotics, Washington, D. C., October 1958.
3. "Dissolving" fatty plaques in arteries. Background on research No. 53. American Heart Association, January 1958.
4. Safar, P., Escarraga, L. A. and Elam, J. O.: A comparison of the mouth-to-mouth and mouth-to-airway methods of artificial respiration with the chest-pressure arm-lift methods. New England J. Med. 258:671-677 (April 3) 1958.

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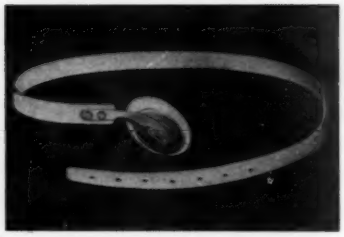

• TRUSS
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DESCRIPTION: Made of white waterproof plastic, this single-spring truss can be adjusted by the patient. It is available in waist sizes 30 to 44, left and right.
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• ILOSONE®

PURPOSE: To provide antibacterial action.
COMPOSITION: Propionate ester of erythromycin.
DOSAGE AND ADMINISTRATION: For adults, 250 mg. every six hours, increased to 500 mg. or more in severe infections; for children, 20 mg. per pound of body weight per day in divided doses, increased to 30 or 40 mg. per pound per day in severe cases.
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PURPOSE: Prevention and treatment of sinus headache.
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N-acetyl-para-aminophenol	150 mg.
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DOSAGE AND ADMINISTRATION: For adults, 2 tablets initially, followed by 1 tablet every four hours, not to exceed 6 tablets in 24 hours; for children 6 to 12 years old, one-half the adult dosage or as prescribed.
HOW SUPPLIED: Bottles of 30.
PRODUCER: Warner-Chilcott Laboratories, Morris Plains, N. J.

(Continued on page A-110)

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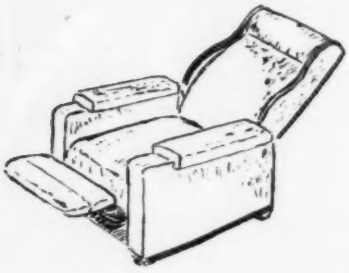
PURPOSE: Antihistaminic, analgesic and antibiotic therapy.
COMPOSITION: Each tablet contains 62.5 mg. V-CILLIN K® and half-strength doses of CO-PYRONIL® (pyrrobutamine compound) and A.S.A.® Compound (acetylsalicylic acid and acetophenetidin compound).
DOSAGE AND ADMINISTRATION: For adults, 2 tablets every six to eight hours.
HOW SUPPLIED: Packages of 50.
PRODUCER: Eli Lilly and Company, Indianapolis.



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DESCRIPTION: Upholstered in white or brown washable BOLTAFLEX® and with foam-rubber cushions on an all-metal frame, this chair has motors located in the legrest, seat and back. These three motors activate the chair to provide a gentle-to-deep controlled massage action. A timer automatically stops the mechanism whenever desired, and a control box is situated within arm's reach of the chair's occupant. Automatically adjustable to posture, the chair is 42 in. high, 35 in. deep and reclines to a length of 66 in.
PRODUCER: Caddie Creations, Chicago.

• FUTURA LINE GENERATORS

DESCRIPTION: This line includes a portable ultrasonic generator, Model 1200 Medi-Sonar (illustrated), and Models 1400-M and 1400-MG Medisine, a low-voltage wave generator and muscle stimulator. Model 1200 Medi-Sonar is equipped with a 7 sq. cm. Brazilian quartz crystal housed in a transducer which provides a cylindrical output pattern free from hot spots. Conforming to exacting specifications, it provides ultrasonic application over a uniform sound field and has ample power output for all general purposes. Model 1400-M has a wide range of uses, extending from treatment of persistent chronic pathologic conditions involving little or no pain to those requiring maximum sedation. Model 1400-MG, which uses both sine and galvanic currents, is identical to 1400-M when used with the current selector in the sine position. In addition, it has a separate galvanic source which furnishes a smooth, filtered, double-rectified direct current; with the current selector in the combining position, the sine current is superimposed on the galvanic current.
PRODUCER: Dallons Laboratories, Incorporated, Los Angeles.

• VCE MICROSCOPE SLIDE

DESCRIPTION: Designed to facilitate the comparative study of cytologic smears, this slide is divided into separate sections for vaginal, cervical and endocervical smears. The three areas are separated by vertical lines and are identified by the letters V, C and E etched into the glass. One end is frosted for easy holding and marking. When three smears are prepared separately on the slide, it is possible to categorize the inflammatory reaction as either diffuse or localized in any one of the three sites.
PRODUCER: Glasco Products Company, Chicago.

(Continued on page A-112)

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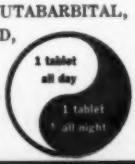

ippyan, A.: J.A.M.A. 168:147, Sept. 13, 1958. 2. Fuller, H. L. and Kassel, L. E.: Antibiotic Med. & Clin. Therapy, 3:322, 1956.

• ISOCLOR

PURPOSE: Nasal decongestant.
COMPOSITION: Each tablet contains 4 mg. chlorprophenpyridamine maleate and 25 mg. *d*-isoephedrine hydrochloride.
DOSAGE AND ADMINISTRATION: 1 tablet three to four times daily.
HOW SUPPLIED: Bottles of 100 and 1000.
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• TAOMID

PURPOSE: Management of urinary tract and upper respiratory infections.
COMPOSITION: Each tablet contains triacetyloleandomycin (TAO®) equivalent to 75 mg. of oleandomycin, and 111 mg. each of sulfadiazine, sulfamerazine and SULFAMETHAZINE®. Each teaspoonful of reconstituted suspension contains triacetyloleandomycin equivalent to 125 mg. oleandomycin, and 167 mg. each of sulfadiazine, sulfamerazine and Sulfamethazine.
DOSAGE AND ADMINISTRATION: For adults, 2 to 3 tablets four times a day, 2 tablets every four hours, or 1 to 2 teaspoonfuls suspension four times a day; for children, ½ to 1 teaspoonful suspension four times a day.
HOW SUPPLIED: Bottles of 60 tablets; powder in 60 cc. bottles.
PRODUCER: J. B. Roerig and Company, division of Chas. Pfizer & Co., Inc., New York.

• KRYL

PURPOSE: To treat sinus and nasal congesti[illegible].
COMPOSITION: Each tablet contains:

Isothipendyl hydrochloride (THERUHISTIN®)	[illegible] mg.
Aspirin	23[illegible] mg.
Acetophenetidin	16[illegible] mg.
l-Phenylephrine hydrochloride	[illegible] mg.
Ascorbic acid	10[illegible] mg.

DOSAGE AND ADMINISTRATION: For adults, 2 tablets initially, followed by 1 tablet every four hours until symptoms disappear; for children 6 to 12 years of age, one-half the adult dosage.
HOW SUPPLIED: Bottles of 100 and 1000.
PRODUCER: Ayerst Laboratories, New York.

• DUOGRAFIN®

DESCRIPTION: Intravenously administered, this contrast medium permits simultaneous visualization by x-ray of both renal and biliary tracts, even after cholecystectomy.
HOW SUPPLIED: 50 cc. vials.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

• PHENISTIX® REAGENT STRIPS

PURPOSE: To detect phenylketonuria in infants.
DESCRIPTION: The reagent-impregnated end of the paper strip is dipped in the urine specimen or pressed against the wet diaper until thoroughly moistened. Any color appearing on the test end within 30 seconds is compared with the color scale on the bottle label.
HOW SUPPLIED: Bottles of 50 strips.
PRODUCER: Ames Company, Inc., Elkhart, Ind.

• BRADOSOL® BROMIDE LOZENGES

PURPOSE: To treat minor infections of the throat and mouth.
COMPOSITION: Each lozenge contains 1.5 mg. dodecyldimethyl (2-phenoxyethyl) ammonium bromide and 2.5 mg. benzocaine.
DOSAGE AND ADMINISTRATION: 1 lozenge dissolved in the mouth as needed.
HOW SUPPLIED: Packages of 24.
PRODUCER: Ciba Pharmaceutical Products, Inc., Summit, N. J.

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stress component
in

rheumatoid arthritis

STRESSCAPS*

Stress Formula Vitamins Lederle

Rheumatologists now look for nutritive failure among patients with arthritis.[1] Vitamin deficiencies and increased need for vitamins in rheumatoid arthritis justify polyvalent vitamin supplementation.[2]

STRESSCAPS restore water-soluble vitamin losses and insure a more desirable response to primary therapy.

each capsule contains:

Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

average dose: 1-2 capsules daily

1. Spies, T. D.: J.A.M.A. 167:675 (June 7) 1958.
2. Robinson, W. D.: Report to A.M.A. Council on Foods and Nutrition, J.A.M.A. 166:253 (Jan. 18) 1958.

*Reg. U.S. Pat. Off.

Lederle LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

News of Interstate

Zollinger President-elect of IPMA

ROBERT M. ZOLLINGER

DR. Robert M. Zollinger, professor and chairman of the department of surgery, Ohio State University, was named president-elect of the Interstate Postgraduate Medical Association at its recent Assembly in Cleveland. Vice-presidents elected at the meeting are Dr. George J. Boines, Wilmington, Delaware; Dr. Kenneth Crawford, Kalamazoo, Michigan, and Dr. George B. McTavish, Winnipeg, Manitoba.

An innovation at the Cleveland Assembly was the cash awards for outstanding research being conducted at teaching institutions within the "host" state. The awards, based on recommendations of the deans of the medical schools in Ohio, were accorded to Dr. Lionel R. King, department of internal medicine, University of Cincinnati College of Medicine, for research on electrolyte metabolism, and to Drs. Mitchell Karlan and Donald W. Traphagen, department of surgery, Ohio State University College of Medicine, for their joint project on localization of upper gastrointestinal hemorrhage with the fluorescin string test.

Also receiving special recognition were three of the scientific exhibits shown. First place award was presented for an exhibit on "Airway obstruction," by Dr. Jay Jacoby and associates, department of anesthesia, Ohio State University College of Medicine; second place award for "Diagnosis and treatment of congenital heart disease," by Dr. Frederick S. Cross and associates, St. Luke's Hospital, Cleveland, and third place award for "Surgical complications of pregnancy," by Dr. Frederick H. Falls and Miss Charlotte S. Holt, Illinois State Department of Health, Chicago.

Other high lights of the Assembly, which attracted the largest attendance of the last few years, included the presentation of a special citation to Mr. Charles F. Kettering* for his contributions to medicine as an inventor and scientist, and of attendance certificates to 21 physicians who have attended 10 meetings of the Association since 1940. All presentations were made at the annual Assembly banquet.

Interstate trustees are now formulating plans for the 1959 Assembly to be held at the Palmer House, Chicago, November 2 to 5.

*This was one of Mr. Kettering's last appearances before his death on November 25.

Dr. Tom D. Spies (*right*), 1958 president of Interstate, is shown presenting a special citation to Mr. Charles F. Kettering for his contributions as an inventor and scientist. Mr. Kettering spoke at the annual banquet of the Association in Cleveland.

Physicians who have attended 10 meetings of the Interstate Postgraduate Medical Association since 1940 received special attendance certificates at the Cleveland Assembly. This group of 20 physicians is in addition to those who received similar certificates at previous meetings. Shown with some of the trustees and officers of the Association are:

Front row *(left to right)*: Dr. J. Mather Pfeiffenberger, Alton, Ill. (trustee and former president); Dr. Samuel F. Marshall, Boston, Mass. (president, 1959); Dr. E. A. Potts, Puente, Calif.; Dr. Edwin S. Hamilton, Kankakee, Ill. (trustee); Dr. Catherine M. Maguire, Pleasantville, N.Y.; Dr. D. A. MacDonald, Minneapolis, Minn.; Dr. I. L. Thompson, West Point, Nebr.

Second row *(left to right)*: Dr. D. S. DiCiro, Olney, Ill.; Dr. W. R. Fraser, London, Ont.; Dr. J. R. Hurley, Daleville, Ind.; Dr. G. B. Callahan, Waukegan, Ill.; Dr. Willis I. Lewis, Herrin, Ill. (trustee); Dr. G. D. Sutton, Flint, Mich.; Dr. A. R. Basinger, North Canton, O.; Dr. J. M. Franklin, Los Angeles, Calif.; Dr. A. S. Burton, Newark, O.

Third row *(left to right)*: Dr. Erwin R. Schmidt, Madison, Wis. (trustee); Dr. Ben T. Whitaker, Boone, Ia. (trustee); Dr. R. G. Arveson, Frederic, Wis. (trustee); Dr. G. R. Fattic, Jr., Niles, Mich.; Dr. P. A. Nierling, Cresco, Ia.; Dr. L. F. Plzak, Berwyn, Ill.; Dr. E. S. Watson, Brookings, S. Dak.; Dr. Donald C. Conzett, Dubuque, Ia. (trustee).

Top row *(left to right)*: Dr. Robert A. Hedgcock, Frankfort, Ind. (vice-president); Dr. Robert N. Larimer, Sioux City, Ia. (trustee); Dr. R. D. Douglas, Jefferson, Texas.

Attendance award recipients not pictured: Dr. J. R. Glazier, Hartford, Conn.; Dr. J. E. Hutchison, Hartford, Conn.; Dr. L. G. Steck, Chehalis, Wash.

IN URTICARIA AND PRURITUS

VISTARIL*

HYDROXYZINE PAMOATE

A PSYCHOTHERAPEUTIC ANTIHISTAMINE

(as designated by A.M.A. Council on Drugs, 1958)

SPECIFIC ANTIHISTAMINIC ACTION in the treatment of a variety of skin disorders commonly seen in your practice.

"While some of the tranquilizers are only partially effective as far as antiallergic activities are concerned . . . [hydroxyzine] has been found, by comparison, to be the most potent thus far . . ."[1]

"The most striking results were seen in those patients with chronic urticaria of undetermined etiology."[2]

PLUS

PSYCHOTHERAPEUTIC POTENCY for the relief of anxiety and tension.

The psychotherapeutic effectiveness of hydroxyzine (VISTARIL) was confirmed in a series of 479 patients suffering from a wide variety of dermatoses, including atopic dermatitis, neurodermatitis, psoriasis, lichen planus, nummular eczema, dyshidrosis, pruritus ani and vulvae, and rosacea. "Adverse reactions were minimal."[3]

RECOMMENDED ORAL DOSAGE: *50 mg. q.i.d. initially; adjust according to individual response.*

VISTARIL Capsules: *25 mg., 50 mg., 100 mg.*

VISTARIL Parenteral Solution: *10 cc. vials and 2 cc. Steraject® Cartridges. Each cc. contains 25 mg. hydroxyzine (as the HCl).*

More than a tranquilizer

REFERENCES:

1. Eisenberg, B. C.: Clinical Medicine *5*:897-904 (July) 1958.
2. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958.
3. Robinson, H. M., et al.: So. Med. J. *50*:1282 (Oct.) 1957.

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PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.*

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F THE URINALYSIS SHOWS INFECTION:

lew Pyridium Tri-Sulfa, for acute urinary tract infections, is the only ombination treatment which provides the therapeutic dose of analgesic yridium with only 1 tablet four times daily. Provides symptom relief n less than 30 minutes plus broad nd efficient antibacterial action. **PYRIDIUM® TRI-SULFA**

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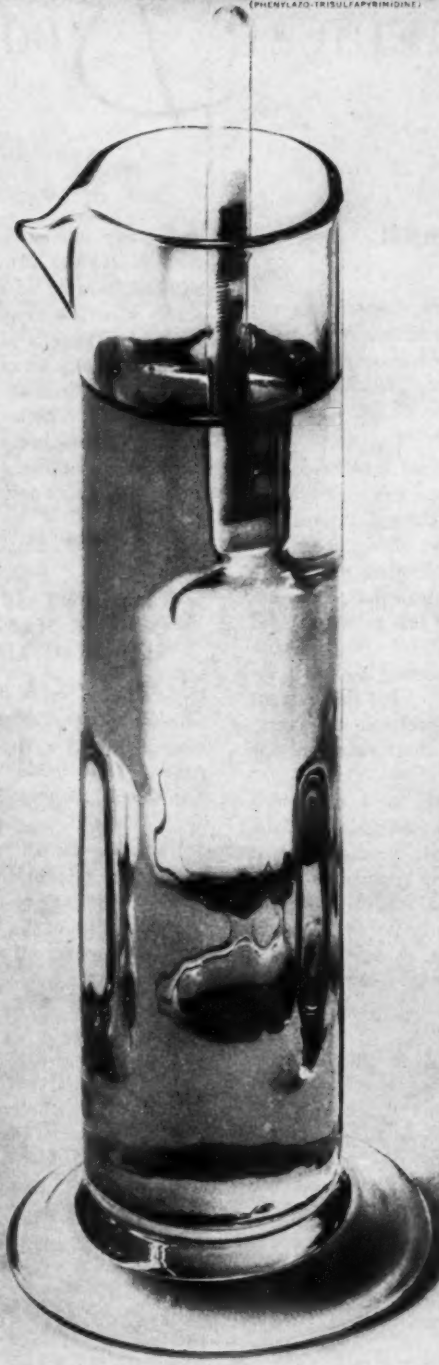

THE MEDICAL Bookman

► ADVANCES IN INTERNAL MEDICINE

Edited by William Dock, M.D., State University of New York College of Medicine, New York, and I. Snapper, M.D., Beth-El Hospital, Brooklyn. Vol. 9. 311 pages, illustrated. 1958, The Year Book Publishers, Inc., Chicago. $7.00.

As is true of each edition of this book, the new volume contains excellent and comprehensive reviews of subjects of current interest by authorities in their respective fields. The first section, dealing with the metabolism of vitamin B_{12}, reviews the absorption, transport, distribution, storage and excretion of this substance and its role in pernicious anemia and other megaloblastic anemias. In the next section a critical review of the literature on the role of the adrenal steroids in the treatment of infection is presented, with the conclusion that their value in this regard is still not known.

The third topic is primary and secondary hyperparathyroidism, with a discussion of the action of parathyroid hormone, the diagnosis of primary hyperparathyroidism, syndromes associated with secondary hyperparathyroidism, and the differential diagnosis of primary and secondary hyperparathyroidism in the presence of renal failure. Although this section is only 20 pages long, it is a noteworthy presentation that merits careful reading and rereading.

Hereditary defects in clotting mechanisms are considered. Following a lucid review of the physiology of blood coagulation and comments on pertinent laboratory procedures is a presentation of the various hereditary conditions with clotting defects, such as hemophilia, Christmas disease, parahemophilia, congenital afibrinogenemia and many others. The following section deals with the typical history, etiology, pathology and clinical features of glomerulonephritis, and includes a review of some aspects of experimental nephritis. There is also an excellent summary of the present-day knowledge concerning carcinoid tumors. The final section deals with some of the renal tubular defects, such as amino-aciduria (including cystinuria and Fanconi's syndrome) and renal phosphaturia, and with the relationship of potassium deficiency to such conditions.

R. V. R.

► CONGENITAL ANOMALIES OF THE HAND AND THEIR SURGICAL TREATMENT

By Arthur Joseph Barsky, M.D., Professor of Clinical Surgery, Albert Einstein College of Medicine, New York. American Lecture Series. 165 pages, 77 illustrations. 1958, Charles C Thomas, Springfield, Illinois. $5.75.

Based on the author's personal experience in 165 cases, this brief but complete monograph gives a clear-cut present-day account of congenital deformities of the hand. A bibliography which completely covers the literature for the past 35 years is included.

The first five chapters review the hereditary and embryologic etiology of the different congenital anomalies; succeeding chapters deal with each anomaly in turn, the most common being discussed first. Each discussion mentions the surgical treatment which in the author's experience has proved most satisfactory.

J. K. M.

(Continued on page A-128)

FURINARY INFECTION PROVES CHRONIC:

Mandelamine is antibacterial, yet is not an antibiotic! Effective in many urinary tract infections resistant to antibiotics and sulfonamides, won't sensitize patients, no resistant strains develop. Mandelamine obviates need for alkalis or forcing of fluids, and it is excellent for long term therapy. Cost is low.

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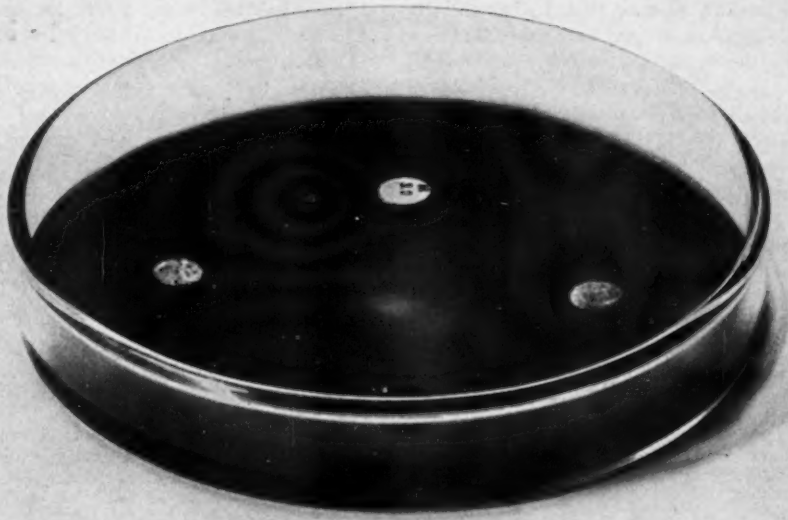

► THE KIDNEY
An Outline of Normal and Abnormal Structure and Function

By H. E. de Wardener, M.D., Senior Lecturer in Medicine, St. Thomas's Hospital, London, England. 338 pages with 74 illustrations. 1958, Little, Brown & Company, Boston. $10.00.

A broad review of current knowledge of the structure and function of the normal and diseased kidney is given in this volume. In a didactic but lucid and readable manner, the author ranges from glomerular structure as revealed by electron microscopy through the major syndromes of renal disease to a consideration of each of the principal diseases of the kidney.

Written for the medical student and practitioner, the book features a diagrammatic presentation of the pathologic anatomy of the kidney. There are no photomicrographs; instead, liberal numbers of drawings depict the glomerulus in health and disease. As a result the student and nonpathologist will obtain a clear if somewhat oversimplified concept of renal pathology.

Special sections deal with renal function during anesthesia and surgical procedures, with the syndromes of tubular dysfunction, and with renal function in various states not directly related to disease of the kidney. The appendix includes valuable material on diuretics, diets, and normal values for renal functional capacity and composition of body fluids. Selected references follow each chapter.

J. C. B.

► THE EYE

By E. Howard Bedrossian, M.D., Assistant Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. 340 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $11.00.

In the preface the author states, "This book was written as a result of repeated requests from residents and colleagues in ophthalmology to copy a loose-leaf handbook which the author carried with him during teaching rounds and clinics." The entire field of ophthalmology is touched on, but no subject is thoroughly discussed. The sections on the basic sciences are the most complete and are intended to be of special help to those preparing for board examinations. Chapters on anatomy, physiology and biochemistry and optics are succeeded by discussions of external and fundus diseases, lens defects, neurologic ophthalmology, ocular injuries and inflammation.

The style of this text, employing the short notes, definitions and classifications of the reference notebook, is useful to the teacher but unusual in a published volume. Reminders rather than descriptive paragraphs are used throughout. This type of manuscript could be expanded into encyclopedic proportions; the cut-off point evidently indicates the extent of the author's interests or his teaching experience. In addition, it is assumed that the reader has a preliminary education in ophthalmology, the basic sciences and general medicine, and the usual text material has been omitted.

The author has packed a great deal of useful information into this small volume, which will serve as a handy reference book for quick review, as a substitute for a good memory, and as a guidebook for clinical class conferences. Residents will keep it under their pillows.

W. L. B.

► THE YEAR BOOK OF MEDICINE (1958-1959)

Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D. and Philip K. Bondy, M.D. 782 pages with 123 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $7.50.

Each year, as internal medicine becomes more complicated and as more articles are published about its various phases, "The Year Book of Medicine" becomes more firmly established as an invaluable aid to the physician who wants to keep up to date on current literature.

As in past editions, the book is divided into sections dealing with infections, diseases of the chest, the blood and blood-forming organs, the heart and blood vessels and the kidney, the digestive system, and metabolism. Each section contains summaries of the recent important papers that have been published on the subject.

The text is well illustrated and contains many helpful editorial comments. This edition will prove as valuable as those which preceded it.

R. V. R.

(Continued on page A-130)

Author of the classic "Bodily Changes in Pain, Hunger, Fear and Rage," pathfinder in experimental physiology,

(1871-1945) demonstrated conclusively the effect of emotions on the G.I. tract.

in G.I. symptoms of anxiety states

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provides relief of pain, spasm, anxiety and tension without belladonna or barbiturates. Side effects are minimal.

each scored tablet contains:
meprobamate 400 mg., tridihexethyl chloride 25 mg.
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1 tablet t.i.d. with meals and 2 tablets at bedtime.

duodenal and gastric ulcer • colitis
spastic and irritable colon • gastric hypermotility • gastritis
esophageal spasm • intestinal colic • functional
diarrhea • G.I. symptoms of anxiety states.

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► CARDIOVASCULAR DISEASES

By David Scherf, M.D., Professor of Clinical Medicine, and Linn J. Boyd, M.D., Professor and Director of Medicine, New York Medical College, New York. Ed. 3. 829 pages with 119 illustrations. 1958, Grune & Stratton, Inc., New York and London. $17.75.

There is good evidence of the widespread approval this book has received in that this is the third English-language edition in 10 years; there also have been many editions in other languages.

The authors emphasize the clinical approach to cardiovascular diseases and stress the value of physical examination rather than instrumental and laboratory methods. The only detailed aspects of the presentation of electrocardiography are a discussion of the role of the exercise test in diagnosis of coronary artery disease and a chapter on disturbances of cardiac rhythm; however, the authors refer to a companion volume on clinical electrocardiography.

In general, the sections on clinical cardiology, physical signs in cardiovascular disease, and the clinical syndromes of acquired heart disease are very good. The section on congenital heart disease is less adequate. With the recent advances in the diagnosis and treatment of congenital heart disease, one would expect a more detailed consideration of the hemodynamic disturbances, at least in those conditions amenable to surgical treatment.

Some statements are made which would not meet with general approval. A contrast between the paroxysmal nocturnal dyspnea in cases of left ventricular failure and that in mitral stenosis is offered without mention of the common factor, namely, left atrial hypertension. The Bernheim syndrome is discussed and is accepted as a possibility without consideration of the data made available by cardiac catheterization which demonstrate the development of pulmonary hypertension in patients with left ventricular failure. It is categorically stated that "the electrocardiogram gives no assistance in the diagnosis of a mitral insufficiency." In the discussion of tricuspid atresia, the authors state that "the success of the Blalock-Taussig operation depends on the size of the atrial septal defect." The reasoning behind this statement escapes this reviewer.

In spite of these criticisms, there is much that is of value in this book for the practicing cardiologist as well as for the student starting his studies. One must agree with the statement in the preface: "A book on cardiology would be an exception indeed if it could not give, even to the expert, some valuable advice."

D. C. C.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

Neurological Basis of Behaviour. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E. and Cecilia M. O'Connor, B.Sc. 400 pages with 109 illustrations. 1958, Little, Brown & Company, Boston. $9.00.

Methods for Research in Human Growth. By Stanley M. Garn, Ph.D., Chairman, Physical Growth Department, Fels Research Institute, Yellow Springs, Ohio, and Zvi Shamir, M.D., Chief Physician, Department of Pediatrics, Hadassah-Hebrew University Hospital and Medical School, Jerusalem, Israel. 121 pages with 30 illustrations. 1958, Charles C Thomas, Springfield, Illinois. $4.75.

The Year Book of Pediatrics. 1958-1959 Series. Edited by Sydney S. Gellis, M.D., Professor and Chairman, Department of Pediatrics, Boston University School of Medicine, Boston. 496 pages with 125 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $7.50.

Emotional Problems of Childhood. Edited by Samuel Liebman, M.D., Clinical Assistant Professor of Psychiatry, University of Illinois College of Medicine, Chicago, with 10 contributors. 176 pages. 1958, J. B. Lippincott Company, Philadelphia and Montreal. $5.00.

Myasthenia Gravis. By Kermit E. Osserman, M.D., Physician-in-Charge, Myasthenia Gravis Clinic, Mount Sinai Hospital, New York. 286 pages with 58 illustrations. 1958, Grune & Stratton, Inc., New York and London. $10.00.

The Recovery Room. American Lecture Series. A symposium by John Adriani, M.D., Professor of Surgery, and John B. Parmley, M.D., Instructor in Surgery, Tulane University School of Medicine, New Orleans. 123 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $4.25.

Pediatric Methods and Standards. Edited by Fred H. Harvie, M.D., Associate Professor of Clinical Pediatrics, University of Pennsylvania School of Medicine, Philadelphia. Ed. 3. 324 pages, illustrated. 1958, Lea & Febiger, Philadelphia. $4.50.

Water and Electrolyte Metabolism in Relation to Age and Sex. Ciba Foundation Colloquia on Ageing. Edited by G. E. W. Wolstenholme, O.B.E. and Maeve O'Connor, B.A. Vol. 4. 327 pages with 85 illustrations. 1958, Little, Brown & Company, Boston. $8.50.

Evolution of the Speech Apparatus. American Lecture Series. By E. Lloyd DuBrul, D.D.S., Associate Professor in Charge of Oral Anatomy, University of Illinois College of Dentistry, Chicago. 103 pages with 20 illustrations. 1958, Charles C Thomas, Springfield, Illinois. $4.75.

For the menopause

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Milprem®-400

400 mg. MILTOWN® + 0.4 mg. CONJUGATED ESTROGENS (equine)

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Miltown acts immediately to

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Conjugated estrogens (equine)

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SUPPLIED: Bottles of 60 tablets.

DOSAGE: 1 tablet t.i.d. in 21-day courses with one week rest periods. Should be adjusted to individual requirements.

Literature and samples on request.

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DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Nov. 1—In the afternoon watching Wisconsin play at football most successfully against Michigan State. In the evening to Judge Braude's for dinner with the Maisons—Lou and George and the ladies—and observed his collection of autographs and of jokes which he has already published in three books. Some samples: "The honeymoon is over when the dog brings you your slippers and your wife barks at you."

William Lyon Phelps: "A cold is both positive and negative; sometimes the eyes have it; sometimes the nose."

Nov. 2—To Fred Hertwig's at the County Hospital and saw Wally Reich, Hoffman, Friedell, Hyman, Blaha, Armstrong, Nechtow and Gasul, and enjoyed talk and food, and football on television, and gave back some of my profit to Wally Reich in gin.

Nov. 3—To the Standard Club for luncheon with Irving Harris, Alex Dworkin and Clarence Cohen to plan for the dedication of a new research facility at Michael Reese. In the evening with the Maisons to the Tavern Club and the opera where "Pagliacci" was sung notably by Di Stefano and also a short sketch called "Gianni Schicchi," which was humorous meat for Tito Gobbi.

Nov. 4—By the early plane to New York after casting my vote on the machine. Reading en route the life of De Maupassant by Francis Steegmuller. In the evening with Milton and Laura Runyon to dine at Henri Soule's new Côte Azur, and the surroundings were better than the food.

Nov. 5—At noon with Bill Lasdon, Max Geffen and Paul Robinson at the Lotos Club to discuss printing and publishing. Then to confer with Fred Baldwin and John Welch at Warwick's and in the evening to drive to Elizabeth, New Jersey, to speak at the banquet of the Society of Surgeons of New Jersey. Here were Walsh, Dave Allman, Elmer Weigel, Vince Butler, Costello, and many more. The jest best received had to do with a man walking down 57th Street in New York. He asked: "How do you get to Carnegie Hall?" The answer, succinct and terrifying: "Practice!"

Nov. 6—Great excitement at the sudden resignation of the editorial staff of *McCall's* and the employment thereby of Herbert Mayes. To visit Morris Plains and all the day with Al Driscoll, Elmer Bobst, Bill Lasdon, Scheele, Robinson, Clark and Whitney, working on *World-Wide Abstracts*. At night with Mistress Pepys to see Peggy Wood and Imogene Coca in "The Girls in 509," written by the author of "The Solid Gold Cadillac." It was full of wit and repartee, but still a trifle.

Nov. 7—For breakfast came Stanley Henwood to speak of international congresses. At noon to luncheon with George Bugbee at the Player's Club and talked of the drama, of medical affairs and public education. Then to interview my publishers. In the afternoon with Bill Frohlich, Bobst, Mandell and Leo Roon to design a program on pharmacy for Arden House. Then came Peter Warren for conferences, and with the Warrens to Danieli's —King of the Cheese *Soufflé*— and afterward to see Helen Hayes shine brightly with Eric Portman in "A Touch of the Poet."

Nov. 8—Out to White Plains where Randy Lasdon performed handsomely in his confirmation. At night to a magnificent celebration of the occasion tendered by the Milton Lasdons, trading tales with Donagher and many others and hearing of Milton Freiwald's trip abroad and Leonard Field's new office; then late to bed.

Nov. 9—Home by plane and found some grandchildren—Pete and Rosemary—were visiting us. Then with Sam Pearlman and Della to a celebration for Louis Mann, who has given 35 years of service to Sinai Temple. Currently he lectures on human nature, quoting old Pepys: "You can't change human nature; you only make it worse."

Nov. 10—At the desk writing lectures, articles, releases, letters and biographical notes. In the evening to dine at Andy's Epicurean Cafe on chicken livers, chicken *paprikash* with *spaetzle*, *polizinkas*, salad with Roquefort dressing, and then with Justin and Ann to hear Birgit Nilsson sing gloriously in "Tristan and Isolde," in fact too well for Karl Liebl, who came in a poor second. But it may well be that the

(Continued on page A-166)

Even with a cold

New long acting[1,2,3]

Rynatan®

Keeps heads crystal clear

10-12 hours with a single oral dose with remarkable lack of side effects[1,2]

Entirely new long acting oral nasal decongestant
chemically and physically different—utilizing the DURABOND* principle[2,3]

Longest relief of any medication
comfort all day or all night with a single oral dose[1]

Remarkable lack of side effects
"...of 311 patients, incidence of side effects was only 2.2 per cent. Evidence of sedation was (only) 1.2 per cent."[4]

Stops excessive post-nasal drip
and resulting night cough, irritation, secondary infection

1. Lawler, E. G. and Limperis, N.M.: Clin. Med. (Dec.) 1958. 2. Medical Science, 3:370-377 (Mar. 25) 1958. 3. Cavallito, C. J. and Jewell, R.: J. Am. Pharm. A. (Scient. Ed.) 47:165-168, 1958. 4. Antibiotic Med. & Clin. Therapy 5:578-581 (Sept.) 1958.

Samples and literature on request

***DURABOND**

A new principle in medicine that controls absorption rather than dissolution or release, independently of gastrointestinal motility or specific pH. Maintains constant rather than sporadic blood levels, hence no over-release or under-release. This gives smooth therapeutic results, rare incidence of side effects. Works even in liquid form for children (Rynatan Suspension).

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RYNATAN TABULES...
For adults and older children

RYNATAN SUSPENSION...
For children (as young as 6 months)

Rynatan contains:	Each tabule	5 cc. suspension
Phenylephrine tannate	25.0 mg.	5.0 mg.
Prophenpyridamine tannate	37.5 mg.	12.5 mg.
Pyrilamine tannate	37.5 mg.	12.5 mg.

Dose: q. 12 h.: Tabules 1-2. Suspension: Children under 6 yrs. ½-1 tsp.; over six 2-3 tsp.

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submergence was by design. The great Rodzinski conducted superbly, bringing from the orchestra tones that moved the emotions of all who heard.

Nov. 11—Veterans' Day, and post office employees took another vacation, which has become their habit nowadays. At noon to the Rotary Club, where Larry Linck told of our work for the crippled. Next to a conference of the program for the City of Hope. To dine with Mistress Pepys at Michael Reese Hospital, planning for their dedication ceremony. Next to the Hall of Fame of the International College of Surgeons to speak on "Epochs in the history of medicine." Here Thorek introduced McIntire, who introduced Ilza Veith, who introduced old Pepys. A large audience bulged the walls and this always inspires the speakers. So chatted with Guy, Mazell, Lash and many more, and rode home content.

Nov. 12—From New York came Joe Mandell on the program of the Arden House conference. So he talked with his classmate Adlai Stevenson, and we lined up many good prospects for the program. In the evening to hear the "Barber of Seville," with Gobbi again giving a superb performance.

Nov. 13—By the morning plane to Washington and drove at once to Salisbury, Maryland, for cocktails with the Benjamins and Grady Hayden, and also partook of some remarkable little chopped chicken rolls. Then on to Crisfield, where the hospital is to be rebuilt. Here viewing the building with Alfred J. Bryan, administrator; it was erected through the philanthropy of the McCreadys, following the death of their little girl in a motor accident in which died also Henrietta Steinbach, who worked with me in the Durand Hospital for Infectious Diseases in Chicago in 1913. At the dinner, A. N. Barr told of an address made by old Pepys at Temple in Philadelphia in 1936. The Governor Tawes reminded old Pepys that Benjamin Willis and R. Schriver of our school board also came from Crisfield. Thereafter driving to Salisbury for the night.

Nov. 14—In Washington after a fast drive from Salisbury and on American again back to Chicago. In the afternoon much work at the desk and at night to hear still another opera, this being "La Traviata," with Steber not at her best and with Simoneau and Bastianini really of the best.

Nov. 15—To Michael Reese to view the new research institute given by Nathan Cummings and other donors. Here Clarence Cohn presided, Carl Wiggers spoke of the history of physiology, and Francis Moore spoke of the history of surgery most eloquently and with a fine philosophy for such a young man. In the afternoon M. Edward Davis gave the Arthur Koff memorial lecture.

Nov. 16—To view the research institute and to participate in a dedication program where Dr. Irv Wolin presided. Speaking were Irv Harris of The Toni Company, Chairman of the Board Nathan Cummings, and old Pepys, who spoke reminiscently of Reese and of medical research. And here greeting Katz, Josephson, Necheles, Saphir, Tannenbaum, Ullmann, Rachmiel Levine, Gold, Milzer and Wolf. The new laboratories are replete with fine technical devices, modern facilities and modernistic paintings which Cummings bestowed. Then at night heard Cummings, interviewed by Norman Ross, tell of his belief in the value of organized research.

Nov. 17—At the desk and in the evening to hear "Boris Godounov" with Boris Christoff and

(Continued on page A-170)

Humor of the Day

"Doctors are generally too busy being doctors to spare the time to play in bridge tournaments. However, they are trained observers. They bring to the bridge table a diagnostic skill that is an invaluable asset in both bidding and play. Many of the physicians with whom I have enjoyed a game have the potential to become bridge greats. But, fortunately for us all, they have chosen to give their talents another direction."—Charles Goren.

This was a preface to a hand described in *Sports Illustrated*, played by Drs. Nathaniel Robin and Irving Kramer, Long Island, with some fine mind reading.

* * *

Wrong Exposure

Henny Youngman heard of a couple so poor they couldn't afford talcum powder for their infant. Henny had no such problem, because he says that when he was a baby, he posed for talcum powder ads, and got a lifetime supply.

"You posed for talcum powder?" another Lindy's habitué asked dubiously. "With *your* face?"

"The face," rejoined Henny, "had nothing to do with it."

* * *

Conversation

Old Pepys: I was in La Grange and saw one of the finest 100 bed hospitals I have ever seen. They had a sign that said "Recovery Room," but they called it the "Intensive Treatment Room."

Walter Kahoe: Reminds me of the sick man at home with a bad prognosis. He asked his wife to have him moved to the "living room."

* * *

"The prompt and effective clearing of organisms and pyuria that was obtained in this series and in a previous one with Gantrisin ***plus*** *the dramatic relief of bladder and urethral symptoms which can be attributed to the [phenylazo-diamino-pyridine HCl] indicated to us that* ***Azo Gantrisin*** *is an ideal compound for use in common urinary tract infections that we see from day to day in the practice of urology."**

The synchronized therapy provided by Azo Gantrisin is highly effective against infections carried by the blood stream and the urine. Valuable also in prophylaxis before and after cystoscopy, catheterization and urologic surgery. *F. K. Garvey and J. M. Lancaster, *North Carolina M. J.*, *18*:78, 1957.

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a fine supporting cast. The orchestra conducted by Sebastian because of the illness of Rodzinski did nobly.

Nov. 18—At noon to the Tavern Club to meet with Austin Smith, Lee Van Antwerp, Ev Lyght, Harold Swanberg and Dean Smiley of the executive board of the American Medical Writers' Association, discussing future plans, scientific awards and similar projects.

Nov. 19—At noon to the Chicago Athletic Club for a meeting of the board of directors of the Lyric Opera, which does well indeed. So here much talk of negotiations with Callas, who has been singing in Dallas, and heard some sage remarks by Eric Oldberg, the neurosurgeon who guides our symphony orchestra. Thereafter by train to Davenport, reading en route a most literate mystery by Stanley Ellin called "The Eighth Circle." In Davenport came by old friends Youngberg, Harkness, Eihl and Balzer. The dinner at Johnny Hartmann's was excellent, and "a pleasant time was had by all," particularly in the apartment of Harkness, where we reminisced of old Rush until midnight.

Nov. 20—Home on the Rock Island, reading a sad tale of Negro boy delinquency called "Corner Boy." At noon to the annual meeting of the Chicago Heart Association, where well-merited citations were conferred on DeWitt Clough and Wakerlin. Wright Adams presided, a movie of progress was shown, and the governors—including old Pepys—were elected. In the evening to the Pearson, where Jack Greenhill and his lady entertained handsomely with pheasant under glass; a magician, Jimmy Thompson, mystified all with sleight of hand and fancy dealing.

SHE GOT DAMAGES—AND DAMAGES

"A woman who found herself locked in a ladies' lavatory at Harlow, Essex, and broke her ankle when she tried to climb out, is to get damages against Harlow Urban Council. She won her case in the Court of Appeals.

". . . the mishap occurred on a morning in January, 1956, when Mrs. Sayers and her husband were going to Olympia by bus. After entering a cubicle in the public convenience she found she could not open the door. She spent 10 minutes trying to attract attention through a window. Then she thought she might escape by climbing over the 7 ft. high door, which had a gap above. She was only 5 ft. 4 in. tall, and when she stood with one foot on the lavatory seat and the other on the toilet fixure she realized she could not do so. In trying to regain the ground she fell. She had put some of her weight on the toilet roll. This, 'true to its mechanical requirement, rotated and disturbed her equilibrium.'"

From the *London Daily Telegraph*

* * *

AT MERCY HOSPITAL

Resident: "Which ward do you want to be taken to? A pay ward, or part-pay or———?"

Ryan: "Any of them, Doc, that's safely Democratic."

* * *

Nov. 21—All this day at the desk with my scrivening and at night to Julian Levi's, the magician who converted a slum into a new magic city. Here were Philip D. Hauser, Watkins, Davis and Braun and Ruth Moore, and the evening passed rapidly with conversation of travel, politics, sociology and philanthropy. Philip Hauser tells great tales of travel in Japan and meetings with the geisha, with side remarks on anatomy.

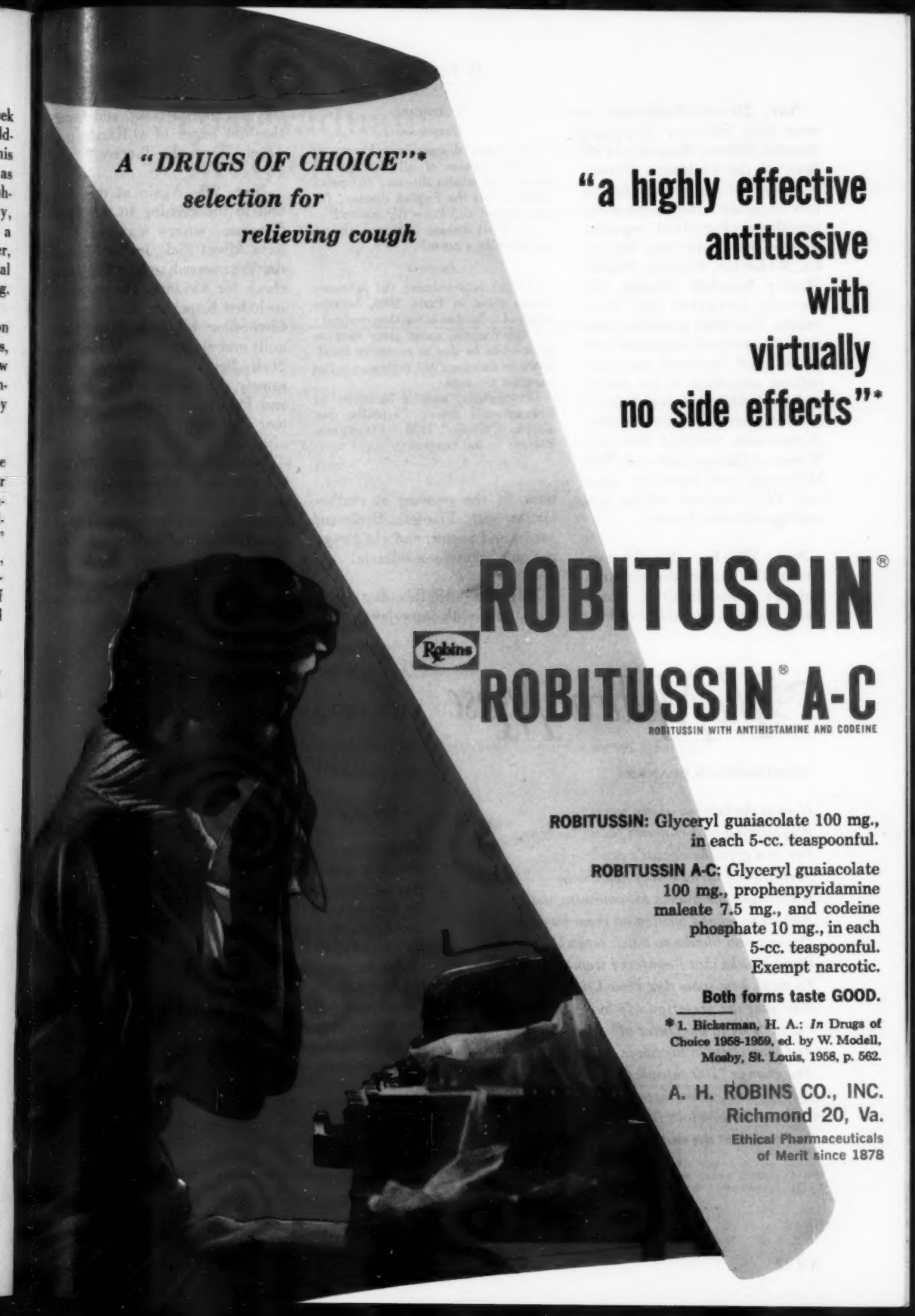
Nov. 22—To Indianapolis for a visit with the home folks. Here at mathematics with the old combatants Meyers, Kahn and Mantel, and did well for the week end. Here also the Lurveys holding a thanksgiving dinner for his recovery, with all the medicos as guests of honor, including Wishard, Nourse, Mertz, Kwitny, Aronson and old Pepys, with a world's record-shattering dinner, much good humor, and convivial chatter until late in the evening.

Nov. 23—Again at luncheon and dinner with the home folks, viewing betimes the great new plant of the J. P. Michaels Company, and late at night back by plane.

Nov. 24—All day again at the desk. In the evening with Lester and Marjorie Marks and teenager Georgia to dine at the Standard Club and to hear "Aida" sung handsomely by Gobbi, Simonata, Bjoerling and Rysanek, with great numbers of marching men and women and ballet dancers.

Nov. 25—By plane to New York and at noon for luncheon with Stan Henwood. Next to confer with Milton Runyon and after that to be interviewed by Galen Drake of CBS. Thereafter to see Herbert Mayes in his new office as editor of *McCall's*. To cocktails at the Plaza, where came Governor Meyner of New Jersey; Lansing P. Shield of Grand Union Co.; Gruber of P. Lorillard Co., with new president Temple; Warburg; Shanks of Prudential; and Phil Houtz of the National Jewish Hospital in Denver, with board chairman Samuels. So Lester L. Wolff of television presided, the citation was presented to Shield, N.J.H. collected $55,000, and old Pepys spoke, after which Al Kelly did double talk and closed the meeting amid howls of laughter.

(Continued on page A-172)



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*1. Bickerman, H. A.: *In* Drugs of Choice 1958-1959, ed. by W. Modell, Mosby, St. Louis, 1958, p. 562.

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Nov. 26—In Washington to meet with Secretary Flemming, Surgeon General Burney and Dr. Bain of the Children's Bureau, working out suggestions for future programs. Here were many presidents of medical organizations—Drs. Gundersen, Barborka, Wakerlin, Charles Shields, Murray Kornfeld, Marble, McGavack, Crabtree and many others. The chief problems were needed personnel, organized care of the aged, improved communications, education of the public, and leadership for coordination and integration of services. Next chatted with Assistant Secretary Wilson of Chicago and with Tom McGavack, and home by Capital's VIP Viscount, sitting and reading with Leo Lyons.

Nov. 27—For this Thanksgiving Day came the children and the grandchildren, which made really a suitable celebration. In the evening at mathematics with Friedell, Hoffman, Justin and Lester, and old Pepys the only winner—a miracle!

QUIZZICAL

Questions

(1) What disease was known as (a) the captain of all the men of death; (b) muslin disease; (c) polka morbus; (d) the English disease; (e) stop, knave, and know thy master?

(2) What disease is named after a character in a poem?

Answers

(1) (a) tuberculosis; (b) influenza (name given in Paris, 1803, because believed to be due to too-thin clothes); (c) tuberculosis, name given because believed to be due to excessive indulgence in dancing; (d) rickets; (e) the sweating sickness.

(2) Syphilis, after a character in Fracastoro's poem, "Syphilis, sive morbus Gallicus," 1530.—Ffrangcon Roberts in the *Lancet*.

* * *

Nov. 28—All this day busy, busy, busy with interviews, writing and similar tasks, and began the 900 pages of O'Hara's new novel "From the Terrace."

Nov. 29—Again at the desk and in the evening to the Pick-Congress, where Variety Club gave Albert Pick, Jr. the Man of the Year award and La Rabida a check for $55,000. The speakers included Kupcinet, Alex Dreyer, Chancellor Kimpton, Bill Margolis and old Pepys. A comedian, Shelly Berman, commented gruesomely on the hazards of flying, and Preston Bradley on the humor of dying.

Nov. 30—Finishing "From the Terrace," which exaggerates sex in living but includes a tremendously realistic portrayal of a certain set in the life of New York and "new deal" Washington. In the evening came John Doctoroff to show his portraits and tell tales.

The Medical Muse

RICHARD ARMOUR

PRESCRIPTION BLANKS

Here is the burden of my song:
Prescription blanks aren't blank for long,
For in a trice the doctor's pen tracks
Across their surface inky hen tracks
Which turn the blanks to something viable
And make what's written on them buyable.
Prescription blanks so much resemble
Blank checks that I confess I tremble
To think how some day some bright crook
May alter the prescription's look,
Put in "Pay to the Order of"
And then write in his name above
And change "100 capsules" to
"$1000" and, when through,
Grab up the precious little blank
And cash it at the nearest bank.

IN AND OUT

I'd like to silence now the doubter.
Why inner offices, and outer?
While patients sit and tap their toes,
Where is it that the doctor goes?
Has he slipped out for lunch, mayhap,
Or does he snatch a little nap?
Has he another patient whom
He's treating in that inner room?
Or has he gone, perhaps, to look
Up symptoms in a well-worn book?
The answer is, to stop your thinking,
The doctor may be in there drinking
Or even praying (it's been done).
It may be work, it may be fun.
If patients just will keep on hopin',
In course of time the door will open
And he'll come back (no telling when)
To stay until he leaves again.